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Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis

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Abstract

Background

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing Guidelines on Allergen Immunotherapy (AIT) for Allergic Rhinoconjunctivitis. In order to inform the development of clinical recommendations, we undertook a systematic review to assess the effectiveness, cost-effectiveness and safety of AIT in the management of allergic rhinoconjunctivitis

Methods

We searched 15 international biomedical databases for published, in progress and unpublished evidence. Studies were independently screened by two reviewers against pre-defined eligibility criteria and critically appraised using established instruments. Our primary outcomes of interest were symptom, medication and combined symptom and medication scores. Secondary outcomes of interest included cost-effectiveness and safety. Data were descriptively summarized and then quantitatively synthesized using random-effects meta-analyses.

Results

We identified 5932 studies of which 160 studies satisfied our eligibility criteria. There was a substantial body of evidence demonstrating significant reductions in standardized mean differences (SMD) of symptom (SMD -0.53, 95%CI -0.63, -0.42), medication (SMD -0.37, 95%CI -0.49, -0.26) and combined symptom and medication (SMD -0.49, 95%CI -0.69, -0.30) scores whilst on treatment that were robust to pre-specified sensitivity analyses. There was in comparison a more modest body of evidence on effectiveness post-discontinuation of AIT, this suggesting a benefit in relation to symptom scores.

Conclusions

AIT is effective in improving symptom, medication and combined symptom and medication scores in patients with allergic rhinoconjunctivitis whilst on treatment, and there is some evidence suggesting that these benefits are maintained in relation to symptom scores after discontinuation of therapy.

Keywords: Allergen, allergy, allergic rhinoconjuctivitis, desensitization, allergen immunotherapy, rhinitis, subcutaneous, sublingual

BACKGROUND

Allergic rhinoconjunctivitis is a very common chronic condition that can result in considerable morbidity and impairment of quality of life.(1,2) The disease is triggered by exposure to seasonal and/or perennial allergens and, depending on the nature of the allergenic trigger(s) and patterns of exposure, symptoms may be persistent or intermittent.(3) Allergic rhinitis is typically characterized by symptoms of nasal obstruction, a watery nasal discharge, sneezing and itching, and there is often (but not invariably) involvement of the conjunctiva (allergic conjunctivitis), which manifests with itching, injection and tearing.(4) There may in addition be an impact on the ability to concentrate, on school and work performance,(5,6) and interference with daily activities and sleep; furthermore, allergic rhinitis is a risk factor for the development of asthma.(7)

Symptoms can, in many cases, be controlled with avoidance measures and pharmacological therapies such as oral, intranasal and topical (ophthalmic) H_1-antihistamines, intranasal corticosteroids and anti-leukotrienes, as mono-therapy or in combination.(8,9) Allergen immunotherapy (AIT) is an additional potential treatment option, particularly for those with more troublesome disease which remains inadequately controlled despite avoidance measures and regular pharmacotherapy.(8–10) The problem of inadequately controlled allergic rhinoconjunctivitis, despite optimal medical treatment, continues to represent a therapeutic challenge in the majority of patients.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing Guidelines on AIT for Allergic Rhinoconjunctivitis and this systematic review has been undertaken in order to inform the formulation of key clinical recommendations. Specifically, we sought to assess the effectiveness, cost-effectiveness and safety of AIT in patients with allergic rhinoconjunctivitis.(11)

METHODS

As our methods have been reported in detail in our published protocol,(12) we confine ourselves to a synopsis of the methods employed.

Search strategy

A highly sensitive search strategy was developed and validated study design filters were applied to search 15 electronic bibliographic databases. The search strategy was developed on OVID MEDLINE and then adapted for the other databases (see Appendix 1, supplementary file for details). In all cases, the databases were searched from inception to October 31, 2015. Additional references were located through searching the references cited by the identified studies, and unpublished work, while research in progress was identified through discussion with experts in the field. We invited experts from a range of disciplines and regions to add to the list of included studies by identifying additional published and unpublished papers they were aware of and research in progress. There were no language restrictions employed; where possible, relevant literature was translated into English.

Inclusion criteria

We focused on studies conducted on patients of any age with allergic rhinoconjunctivitis investigating the effect of AIT. See Box 1 for full details.

Patient characteristics	Studies conducted on patients of any age with a physician-confirmed diagnosis of allergic rhinoconjunctivitis or allergic rhinitis, plus evidence of clinically relevant allergic sensitization (e.g., skin prick test or specific-IgE).
Interventions of interest	AIT for different allergens (e.g. pollen, house dust mites (HDM), animal dander, cockroach and molds), including modified allergens, administered through the subcutaneous (SCIT), sublingual (SLIT), intralympahtic (ILIT) or any other routes.
Comparator	Placebo or any active comparator.
Study designs	*Effectiveness:* Robust double-blind RCTs. Originally, we planned to include data from any RCT, irrespective of whether there was blinding. This was changed due to the volume of RCT studies. This decision was made prior to any analyses being undertaken. *Cost-effectiveness:* health economic analysis. *Safety:* double-blind RCTs and large case series (≥300 patients).
Study outcomes	*Primary outcomes:* effectiveness, both short-term (i.e. during treatment) and long-term (i.e. at least a year after discontinuation of AIT) as assessed by symptom and/or medication scores.

	Secondary outcomes: disease specific quality of life (QoL); threshold of allergen exposure to trigger symptoms on allergen challenge or in an environmental exposure chamber; health economic analysis from the perspective of the health system/payer; and safety as assessed by local and systemic reactions in accordance with the World Allergy Organization's (WAO) grading system of side-effects.(14,15)
Exclusion criteria	Reviews, discussion papers, non-research letters and editorials, animal studies and studies not employing double-blind RCT designs.

Box 1. Inclusion and exclusion criteria

Study selection

All references were uploaded into the systematic review software DistillerSR and underwent initial de-duplication. Study titles were independently checked by two reviewers (SD and UN) according to the above selection criteria and categorized as included, not included or unsure. For those papers in the unsure category, we retrieved the abstract and re-categorized as above. Any discrepancies were resolved through discussion and, if necessary, a third reviewer (AS) was consulted. Full text copies of potentially relevant studies were obtained and their eligibility for inclusion independently assessed by two reviewers (SD and UN). Studies that did not fulfil all of the inclusion criteria were excluded.

Quality assessment strategy

Quality assessments were independently carried out on each study by two reviewers (UN, SA, AA, MA or TM) using a range of instruments. RCTs were assessed for generation of allocation sequence, concealment of allocation, baseline outcome measurements, baseline characteristics, incomplete outcome data, blinding of outcome assessor, protection against contamination, selective outcome reporting and other risks of bias using the Cochrane Risk of Bias (ROB) Tool.(13) We used the Critical Appraisal Skills Programme (CASP) Economic Evaluation Checklist for health economic studies.(14) For case series, we used the quality assessment tool produced by the National Institute for Health and Clinical Excellence (NICE).(15) Any disagreements were resolved through discussion and, if necessary, a third reviewer (SD or AS) was consulted.

Data extraction, analysis and synthesis

Data were independently extracted onto a customized data extraction sheet in DistillerSR by two reviewers (UN, SA, AA, MA, SD or TM), and any discrepancies were resolved by discussion or, if agreement could not be reached, by arbitration by a third reviewer (SD or AS). A descriptive summary with detailed data tables was initially produced to summarize the literature. Where clinically and statistically appropriate, meta-analyses were undertaken using random-effects modeling.(16) Data were extracted from primary studies, but where these were not available in a suitable format we first contacted authors for data and then if data were still not available we extracted data from previous Cochrane reviews. For outcomes for which it was not possible to produce a meta-analysis, we narratively synthesized data. Heterogeinity statistics are reported with each forest plot.

Sensitivity analyses and assessment for publication bias

Sensitivity analyses were undertaken for the primary outcomes by comparing the summary estimates obtained by excluding studies considered to be at high ROB.

Publication bias was assessed for these same primary outcomes through the creation of funnel plots, and tested by Egger's regression test and Begg's rank correlation test.(17,18)

Subgroup analyses

A number of subgroup analyses were undertaken, which are listed in the protocol.

Registration and reporting

This review is registered with the International Prospective Register of Systematic Reviews (PROSPERO): http://www.crd.york.ac.uk/prospero/. The registration number is CRD42016035373. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist has been used to guide the reporting of this systematic review: http://www.prisma-statement.org/ (Appendix 2, Supplementary file).

RESULTS

Our search strategy yielded 5,932 titles of which 161 studies (reported in 166 papers) met our overall review eligibility criteria. These eligible papers included 135 double-blind RCTs, 19 health economic analyses and seven case series (Figure 1).

Effectiveness

Description of trials

We identified 61 SCIT RCTs (reported in 63 papers) (19–81) including 6,379 patients, 71 SLIT RCTs (reported in 75 papers) (82–119,119–121,121–156) including 13,636 patients and two ILIT RCTs (157,158) including 56 patients (Tables 1a-c). The majority of studies only included adult participants. A range of allergens were assessed including weed, tree and grass pollens, moulds, cat and dog dander and house dust mites. A range of AIT protocols were utilized. The overwhelming majority of trials only reported on short-term effectiveness (Tables S2a-c). A full description of the trials is given in the online supplement.

Quality assessment

SCIT

Overall, the quality of included studies was high. Thirty-seven studies were found to be at low ROB, eight studies at high ROB, and 16 were judged at unclear ROB (Table S2d).

SLIT

The quality of studies was assessed to be low ROB in 26 studies, high ROB in 16 studies and unclear ROB in 28 studies (Table S2e). In one study, ROB could not reliably be assessed from the translation.

ILIT

Both studies had a low ROB (Table S2f).

Primary outcomes

Data on primary outcomes are summarized in Tables S2 g-i .

Symptom scores

Short-term

105 studies reported on the short-term effectiveness of AIT administered by the SCIT (n=51), SLIT (n=52) and ILIT (n=2) routes assessed by symptom scores.

We were able to pool data from 58 SCIT and SLIT studies assessing the effectiveness of AIT by symptom scores. This showed a standardized mean difference (SMD) of -0.53 (95%CI -0.63, -0.42) this suggesting a moderate effect in favor of AIT (Figure 2).

Sensitivity analysis

Sensitivity analysis was performed excluding all studies at high ROB, which demonstrated a SMD of -0.57 (95%CI -0.68,-0.46) (Figure S1, Supplementary file)

Assessment for publication bias

There was evidence of potential publication bias (Figure S2, Supplementary file) which was also suggested by the Begg (P=0.003) and Egger (P=0.003) tests.

Subgroup analyses

Subgroup analyses were undertaken to compare:

- SCIT versus SLIT: SMD -0.65 (95%CI -0.86, -0.43) for SCIT and SMD -0.48 (95%CI -0.61, -0.36) for SLIT (Figures 3a and b), these both showing evidence of benefit; data from the two ILIT trials could not be pooled, but these studies also demonstrated an improvement in short-term symptom scores.
- Children versus adults for AIT (SCIT and SLIT): SMD -0.25 (95%CI -0.46, -0.05) for children and SMD -0.56 (95%CI -0.70, -0.42) for adults (Figures 4a and b), these analyses showing evidence of benefit in both adults and children.
- Children versus adults for SLIT only: SMD -0.42 (95%CI -0.63, -0.21) for children and SMD -0.47 (95%CI -0.64, -0.29) for adults (figures S3a and b), these analyses showing benefit in both adults and children.
- Seasonal versus perennial allergens: SMD -0.37 (95%CI -0.45, -0.28) for seasonal and SMD -0.91 (95%CI -1.47, -0.36) for perennial (Figures S4a and b, Supplementary file), these demonstrating evidence of benefit from both approaches.
- Seasonal versus perennial allergens for SCIT: SMD -0.49 (95%CI -0.72, -0.27) for seasonal and SMD -1.59 (95% CI -2.44, -0.74)for perennial (results from only one study) (Figures S5a and b, Supplementary file), these demonstrating evidence of benefit from both approaches.

- Seasonal versus perennial allergens for SLIT: SMD -0.35 (95%CI -0.45, -0.26) for seasonal and SMD -0.81 (95%CI -1.41, -0.20)for perennial allergens (Figures S6a and b, Supplementary file)
- Pre-/co-seasonal versus continuous treatment in SCIT for pollen: SMD -0.51 (95%CI -0.63, -0.38) in pre/co-seasonal and SMD -0.69 (95%CI -1.09, -0.29) (Figures S7a and b, Supplementary file), these analyses demonstrating evidence of benefit from both approaches.
- Pre-/co-seasonal versus continuous treatment in SLIT for pollens : SMD -0.40 (95%CI -0.48, -0.32) in pre-/co-seasonal and SMD -0.55 (95%CI -0.98, -0.11) in continuous (Figures S8a and b, Supplementary file), these analyses demonstrating a clear benefit associated with both approaches.
- Modified allergen extracts (allergoids) versus unmodified allergen extracts in SCIT: SMD -0.60 (95%CI -0.89, -0.31) versus SMD -0.65 (95%CI -0.93, -0.36) (Figures S9a and b, Supplementary file), these analyses demonstrating evidence of benefit from both modalities
- Aqueous solutions versus tablets in SLIT: SMD -0.41 (95%CI -0.65, -0.18) in aqueous and SMD -0.56 (95% CI -0.80, -0.33) with tablets (Figures S10a and b, Supplementary file), these analyses confirming benefit with both preparations.
- Different allergens for AIT (SCIT and SLIT): HDM: SMD -0.73 (95%CI -1.37, -0.10); grass: SMD -0.45 (95%CI -0.54,-0.36); tree: SMD -0.57 (95%CI -0.92, -0.21); molds: SMD -0.56 (95%CI -2.29, 1.18); weeds: SMD -0.68 (95%CI -1.06, -0.30), these showing that AIT was clearly effective for all allergens except molds for which there was evidence suggestive of benefit but this was imprecisely estimated (Figures S11a, b, c, d and e, Supplementary file),

Long-term

In order to investigate long-term effectiveness, a number of investigators studied a discontinuation period following trials that involved randomization to AIT or placebo in which the superiority of AIT was confirmed. In this longer-term phase, patients were followed-up and outcomes were then again assessed at least one year post-discontinuation of AIT.

There were four trials that studied this outcome, one SCIT (42) and three SLIT (89,114,133), all of which were judged to be at low ROB. Meta-analysis of data was not possible. A full descriptive summary of the main findings are provided in the supplement. In summary, all four trials at low ROB found a beneficial effect on the long-term effectiveness of AIT on symptom scores.

Medication scores

Short-term

89 studies reported on the short-term effectiveness of AIT administered by the SCIT (n=46), SLIT (n=42) and ILIT (n=1) routes on medication scores.

We were able to pool data from 45 SCIT and SLIT trials. This showed an overall SMD of -0.38 (95%CI -0.49, -0.26), this suggesting a small-to-medium effect in favor of AIT in improving medication scores (Figure 5).

Sensitivity analyses

Sensitivity analysis, performed by excluding all studies at high ROB, gave an SMD of -0.35 (95%CI -0.46, -0.24) (Figure S12, Supplementary file).

Assessment of publication bias

The Funnel plot revealed evidence of potential publication bias (Figure S13, Supplementary file) which was also suggested by the Begg (P=0.004) and Egger (P=0.03) tests.

Subgroup analyses

Subgroup analyses were undertaken to compare:

- SCIT versus SLIT: SMD -0.52 (95%CI -0.75, -0.29) for SCIT and -0.31 (95%CI -0.44, -0.18) for SLIT (Figures 6a and b), these analyses demonstrating that both routes were effective.
- Children versus adults: SMD -0.21 (95%CI -0.42, 0.01) for children and SMD -0.43 (95%CI -0.56, -0.30) for adults (Figure S14a and b, Supplementary file), these showing a clear benefit in adults and the suggestion of benefit in children (but this was not confirmed)
- Children versus adults for SLIT only: SMD -0.60 (95%CI -1.12, -0.07) for children and SMD -0.45 (95%CI -0.69, -0.22) for adults showing a benefit in both. (Figure S15a and b, Supplementary file)
- Seasonal versus perennial allergens for AIT (SCIT and SLIT): SMD -0.30 (95%CI -0.43, -0.16) for seasonal and SMD -0.63 (95%CI -1.12, -0.15) for perennial allergens (Figure S16a and b, Supplementary file), these indicating that both were effective.

- Seasonal versus perennial allergens for SCIT: SMD -0.77 (95% CI-1.28, -0.25) for seasonal and SMD -0.27 (95%CI -1.01, 0.48) for perennial (results from only one study) (Figure S17a and b, Supplementary file)
- Seasonal versus perennial allergens for SLIT: SMD -0.24 (95% CI -0.38, -0.10) for seasonal, SMD -0.72 (95% CI -1.30, -0.13) (Figure S18a and b, Supplementary file), indicating that both were effective.
- Pre/co-seasonal versus continuous treatment in SCIT for pollens: SMD -0.40 (95%CI -0.56, -0.25) in pre-seasonal and SMD -1.23 (95%CI -2.34, -0.12) in continuous (Figure S19a and b, Supplementary file), these indicating that both were effective.
- Pre-/co-seasonal versus continuous treatment in SLIT for pollens: SMD -0.30 (95%CI -0.42, -0.18) in pre-/co-seasonal and SMD 0.00 (95%CI -0.32, 0.33) for continuous (Figure S20a and b, Supplementary file), these analyses suggesting that pre-/co-seasonal was effective and that continuous treatment was ineffective.
- Modified allergen extracts (allergoids) versus unmodified allergen extracts in SCIT SMD -0.94 (95%CI -1.73, -0.16) versus SMD -0.44 (95%CI: -0.64, -0.24) (Figure S21a and b, Supplementary file),
- Aqueous solutions versus tablets in SLIT: SMD -0.35 (95%CI -0.55, -0.14) for those receiving aqueous and SMD -0.42 (95%CI -0.64, -0.19) for tablets (Figure S22a and b, Supplementary file), these analyses showing that both preparations were effective.
- Different allergens for AIT (SCIT and SLIT): HDM: SMD-0.63 (95%CI -1.12, -0.15)) vs Grass: SMD-0.32 (95%CI -0.46, -0.18) vs Tree: SMD -0.40 (95%CI -0.59, -0.20) vs Molds: SMD 0.34 (95%CI -0.41, 1.09)(results from only one study) vs Weeds: SMD -0.44 (95%CI -0.80, -0.09) (Figures S23a, b, c, d and e, Supplementary file), these showing evidence of benefit for all allergens except molds.

Long-term

There were three low ROB trials that assessed this outcome: one SCIT (42) and two SLIT. (114,133) These three trials are described in detail in the supplement. Overall, one trial found a benefit of AIT (SCIT) on long-term medication scores; the two other SLIT trials did not show a sustained effect.

Combined symptom and medication scores

Twenty-nine studies reported on the short-term effectiveness of AIT administered by the SCIT (n=20) and SLIT (n=9) routes on combined symptom and medication scores. Two studies (one SCIT and one SLIT) reported on long-term effectiveness in relation to this outcome.

Short-term

We were able to pool data from 15 studies. Meta-analysis found a SMD of -0.49 (95%CI -0.69, -0.30), this suggesting a small-to-moderate effect in favor of AIT (Figure 7).

Sensitivity analysis

No sensitivity analysis was possible as no studies were judged to be at high ROB.

Publication bias

The funnel plot showed evidence of potential publication bias, (Figure S24, Supplementary file) which was also suggested by the Begg (P=0.005) and Egger (P=0.03) tests.

Subgroup analyses

Subgroup analyses were undertaken to compare:

- SCIT versus SLIT: SMD -0.51 (95%CI -0.77, -0.26) for SCIT and SMD -0.47 (95%CI -0.81, -0.12) (Figures 8a and b), these analyses showing a benefit from both SCIT and SLIT.
- Children (<18) versus adults (≥18 years) for AIT (SCIT and SLIT): SMD -0.85 (95% CI -1.52, -0.17) (results from one study only) for children and SMD -0.44 (95%CI -0.65, -0.22) for adults (Figures S25a and b, Supplementary file), these analyses showing a benefit in both children and adults
- Pre/co-seasonal (short term treatment) versus continuous treatment in SCIT for pollen: SMD -0.41 (95%CI -0.58, -0.24) for pre-seasonal and SMD -0.86 (95%CI -1.49, -0.22) for continuous (results from one study only) (Figures S26a and b, Supplementary file), these analyses showing a clear benefit from pre/co-seasonal treatment and the suggestion (but not confirming) benefit from continuous treatment
- Modified allergen extracts (allergoids) versus unmodified allergen extracts in SCIT: SMD -0.49 (95%CI -0.79, -0.19) for allergoids and SMD -0.36 (95%CI -0.73, 0.03) (Figures S27a and b, Supplementary file), these finding a clear benefit from allergoids and suggesting (but not confirming) a benefit from unmodified preparations.
- Different allergens for AIT (SCIT and SLIT): Grass: SMD -0.41 (95%CI -0.58, -0.24) vs Tree (one study only): SMD -0.26 (95%CI -0.64, 0.13) vs Molds: SMD -0.65 (95%CI -2.06, 0.76) vs Weeds: SMD -0.69 (95%CI -1.24, -0.13) (Figures S28a, b, c and d Supplementary file), this

showing clear evidence of benefit for grass and tree pollens, and suggesting (but not confirming) evidence of benefit for molds and weeds..

Long-term

We found one SCIT trial (53) and two SLIT trials (109,133)that reported on this outcome. These are described in detail in the supplement. Overall, one of the three trials found evidence of a sustained beneficial effect on combined symptom and medication scores. The one trial at an unclear ROB (Didier 2013/2015) demonstrated a two year carry over effect of AIT in the active SLIT group that received AIT four months pre-seasonally for three consecutive seasons but not for the group which received AIT two months pre-seasonally.(109,159)

Secondary outcomes

Disease-specific quality of life

Thirty studies reported data on quality of life (QoL): these comprised of SCIT (n=17) (19,20,23,28,33, 34,35,45,46,55,58,68–70,72,74,79) and SLIT (n=13) (90,99,104,106,108,110,117,129,130,132,140,145,149) trials (Tables S2j and k). The majority of trials (n=29) used one of the disease-specific, validated Rhinitis Quality of Life Questionnaire (RQLQ) instruments. However, one SLIT study (eligible because it reported on other outcomes) used a generic, non-disease specific tool, the SF-36, and this was therefore not considered further.(140) Due to inconsistencies of reporting data, it was not possible to pool results from all of the studies and no SLIT studies were suitable for inclusion in meta-analysis. Pooling data from the six SCIT studies with suitably reported data derived from the original and standardized RQLQ instruments found a SMD of -0.35 (95%CI -0.74, 0.04), this corresponding to a likely small-to-medium improvement in the AIT group when compared to placebo (Figure 9).

Allergen challenge models in AIT

A detailed description of environmental exposure chamber, nasal and conjunctival challenge studies are described in the supplement. One SCIT and three SLIT (83,120,121) chamber studies demonstrated the effectiveness of AIT. Results of nasal challenge studies for 15 SCIT (23,24,27,29,30,33,37,43,52,57–59,63,64,75) and 11 SLIT (84,86,87,92,93,122,128,136,139,146,150) (Table S2l) were conflicting making it difficult to make clear conclusions. There was no clear evidence of effectiveness in 12 SCIT (21,23,35,38,42,45,55,62-64,70,72) and four SLIT conjunctival challenges studies (120,127,138,146) (Table S2m).

Cost-effectiveness

Characteristics of studies

We identified 19 eligible studies that reported on health economic evaluations of SCIT and SLIT in both children and adults (Table S2n).(160–178) Studies were based in a range of countries. Seven of the studies reported results against disease specific outcome measures whilst the remaining 12 reported results based on quality adjusted life years (QALYs). Thirteen of the studies were based on RCT data or meta-analyses of RCT data(160–169,176–178). Full details are in the supplement.

Quality appraisal

The quality appraisal of the included studies is detailed in Table S2o.

Main findings

In general, the studies found that AIT, and where defined both SLIT and SCIT, were more effective than standard care including pharmacotherapy, but also more expensive. The studies that compared SLIT with SCIT gave very mixed results not allowing a clear conclusion to be drawn that either treatment was necessarily more effective or more costly than the other from a health system perspective. The studies comparing Grazax (SLIT) and Oralair (SLIT) suggested that Oralair is both more effective and cheaper than Grazax.(165,167)

For those studies based on RCT data conducted from a health system perspective and using QALYs as their outcome measure (n=7), we found that:

- Nasser 2008: In patients with both rhinitis and asthma in England the incremental cost-effectiveness ratio (ICER) for SLIT versus standard care was £8816 (€10851) per QALY at 2005 prices inflated using national health service (NHS) inflation indices (i.e. Personal Social Services Research Unit (PSSRU)) to £10726 (€13202) per QALY at 2014/15 prices. (177)
- Poulsen 2008: In adult patients with rhino-conjunctivitis in Denmark the ICER for SLIT versus standard care was 134105 DKK per QALY (no price year was given so we assumed study year of 2008) updating to current prices and £ at 0.1 £ per DKK gave an ICER of £15294 (€18824) per QALY at 2014/15 prices.(164)
- Keiding 2007: In adult patients with rhino-conjunctivitis in Austria, Denmark, Finland, Germany, Netherlands, Sweden the ICERs of SCIT compared to standard care in 2005 Euro per QALY

were 9716, 2586, 13683, 10300, 24519 and 22675, respectively. Updating to current prices and £ at 0.75 GBP per Euro gives ICERs of £8866, £2360, £12486, £9399, £22374 and £20691 per QALY respectively at 2014/15 prices.(162)

- Ronaldson 2014: In 5-16 year olds with rhino-conjunctivitis with or without asthma in the UK the ICER for SLIT versus standard care was £12168 (€14976) per QALY at 2008 prices. Updating to current prices gives an ICER of £13357 (€16440) per QALY at 2014/15 prices.(166)
- Westerhout 2012: In patients with rhino-conjunctivitis without asthma in Germany the ICER for SLIT (Oralair) versus standard care was 14728 euros per QALY at 2011 prices. Converting to current prices and GBP at 0.75 £ per Euro gives an ICER of £11460 per QALY.(167)
- Verheggen 2015: In patients with rhinoconjunctivitis without asthma in Germany the ICER for SLIT (Oralair) versus SCIT is 12593 euros per QALY at 2013 prices. Converting to 2014/15 prices and GBP at 0.75 GBP per Euro gives an ICER of £9627 per QALY(168)
- Reinhold 2016: In patients with rhinoconjunctivitis without asthma in Germany SCIT (Allergovit) is cheaper and more effective than SLIT (Oralair). The ICER for SCIT (Allergovit) standard care is 11000 euros per QALY at 2013 prices. Converting to 2014/15 prices and GBP at 0.75 GBP per Euro gives an ICER of £8334 per QALY.(169)

When assessing these results, it was unclear how comparable the patient populations were between the studies; a key factor that impacts the costs and quality of life observed is the proportion of patients who have asthma as well as rhinitis – these proportions were not reported in the studies. Also noteworthy was that the ICERs for AIT seemed to vary substantially between different health systems as demonstrated in Keiding et al 2007 where ICERs range from £2360 per QALY in Denmark to £22374 per QALY in the Netherlands suggesting that straightforward conclusions may not be generalizable even across seemingly similar countries.(162)

Overall interpretation

The seven key studies identified, disregarding the caveats about generalizability, suggested that SLIT and SCIT treatment would be considered cost-effective in this patient population in England at the standard NICE cost-effectiveness threshold of £20,000 (€24616) per QALY. However, the quality of the studies and the general lack of attention to characterizing uncertainty and handling missing data need to be taken into account when interpreting these results.(162,164,166–169,177)

Safety

RCTs and case-series were eligible for inclusion to consider the safety of AIT.

Randomized controlled trials

Safety data for SCIT and SLIT RCTs are summarised in Tables S2p-v. There was a great variation in reporting of adverse events and a number of grading scales including WAO and EAACI were used. As detailed in the tables some studies reported limited or unclear data on number of AEs, some studies reported no data on AEs and others reported that no AEs occurred at all through the duration of the trial period. Conversely some studies reported all treatment emergent AEs.

Total adverse events

We were able to pool data for this outcome for total number of adverse events. Safety data for 51 SCIT and SLIT RCTs were pooled to give an overall risk ratio (RR) of experiencing an adverse event (AE) of 1.64 (95%CI:1.43, 1.89).(Figure S3a)

For SCIT studies (n=19), we found an RR of 1.58 (95%CI:1.13, 2.20) of experiencing an AE and for SLIT studies (n=32) an RR of 1.68 (95%CI:1.44, 1.98).(Figures S3b and c) suggesting a comparable safety profile for both modes of AIT.

Systemic adverse events

We were able to pool data for number of systemic AEs for 39 SCIT and SLIT RCTs to give an overall RR of experiencing a systemic AE of 1.26 (95%CI:1.03, 1.55).(Figure S3d) For SCIT studies (n=15), we found a RR of 1.15 (95%CI: 0.67, 2.00) of experiencing a systemic AE and for SLIT studies (n=24) a RR of 1.31(95%CI: 1.05, 1.63).(Figures S3e and f)

We were able to pool data for the number of patients experiencing a systemic AE for SCIT and SLIT RCTs (n=18) to give a RR of 2.37 (95% CI: 1.09, 5.16). (Figure S3g)

Local adverse events

We were able to pool data for local AEs for 39 SCIT and SLIT RCTs to give an overall RR of experiencing a local AE of 1.78 (95%CI 1.51, 2.11).(Figure S3h) For SCIT studies (n=9), we found an RR of 2.21 (95%CI 1.43, 3.41) of experiencing a local AE and for SLIT studies (n=30) an RR of 1.71(95%CI 1.43, 2.05).(Figures S3i and j)

We were able to pool data for the number of patients experiencing a local AE for SCIT and SLIT RCTs (n=17) to give a RR of 1.72 (95% CI:1.32, 2.23) (Figure S3k)

Case series

Seven large case series were identified.(179–185) (Tables S2w-y) Local (LR) and systemic (SR) AEs were recorded in a range of treatment protocols, including conventional, rush, ultra-rush and cluster. In total 4045 patients were included in these case series however only 3541 were patients with allergic rhinoconjunctivitis; we therefore focused on data for these patients.

The case series were conducted in a number of countries including Spain, Colombia, US, Germany and Portugal.

The case series highlighted that where modified allergen extracts were used to deliver AIT this was safer in terms of number of AEs reported compared to unmodified extracts. (180–183)

Safety data from the rush (180) and ultra-rush (181,182) protocols were evaluated and are presented in Tables S2v and w. The studies concluded that the frequency of SRs were similar to conventional build-up schedules, but importantly rush and ultra-rush protocols were associated with improved patient adherence to treatment by reducing the number of injections required and the cost associated with treatment. Comparable benefits of cluster treatment protocol were also reported in one study. (184) Finally, one case series looked at investigating the number of AEs where patients received either conventional or cluster IT via the SLIT route. AEs were reported in 0.15% of all administered doses in which 9.3% of patients experienced a SR. The study concluded that SLIT was safe in the treatment of allergic rhinoconjunctivitis. (179)

No fatalities were reported in any of these studies.

DISCUSSION

Statement of principal findings

This review of a very substantial body of international trial evidence, many of which were judged to be at low ROB, has found clear evidence that AIT improved all three of our primary outcomes – i.e. symptom, medication, and combined symptom and medication scores over the short-term. These findings were robust to pre-specified sensitivity analyses but evidence of potential publication bias was identified for all three primary outcomes. Although the long-term studies are fewer in number, there was a modest evidence-base in support of the effectiveness of AIT in improving symptom scores after treatment discontinuation for both SCIT and SLIT. The evidence was less clear in relation to the impact on medication and combined symptom and medication scores. SCIT improved disease specific quality of life. We could draw no clear conclusions on the effectiveness of AIT on nasal and conjunctival challenges and on cost-effectiveness which may be cost-effective in an English NHS setting, but due to the poor quality of the studies this needs to be interpreted with caution. AIT increased the risk of adverse events for both SCIT and SLIT, but no fatalities occurred.

Strengths and limitations

To our knowledge, this is the most comprehensive assessment of AIT in allergic rhinoconjunctivitis ever undertaken. We employed internationally accepted techniques to systematically identify, assess and synthesize a substantial body of evidence. This involved taking advantage of and building on other recent systematic reviews focusing on distinct modes of delivering AIT.

The limitations of this review need to be considered. First, despite our extensive searches we may not have uncovered all relevant evidence on this subject. Second, we were limited by the heterogeneity in approaches used to assess outcomes, which meant we were unable to pool data from all trials or undertake all the planned subgroup analyses. Furthermore studies for which data was pooled also showed heterogeneity which may be related to the diverse populations studied, protocols followed, products used and duration of trial period. For the subgroup analyses that were undertaken, there was in some cases imprecision which impacted on our ability to draw clear conclusions. These subgroup analyses were indirect comparisons between SCIT and SLIT and the fidnings should therefore be cautiously interpreted. Third, because of the heterogeneity in scoring systems used, we undertook meta-analyses using random-effects modelling and pooled data using SMDs, which can be difficult to interpret. The absolute size of the SMD was used to guide assessment of the likely effect size demonstrated.(186) Finally, it needs to be borne in mind that there may have been important differences in effectiveness between specific AIT products. Investigating this issue was however beyond the scope of this review. In

terms of safety there was heterogeneity in reporting of adverse events with many differing scoring systems used due to this we were unable to report this outcome as originally planned using only the WAO grading system.

Implications for policy, practice and research

Our findings clearly show that AIT is effective in improving the three patient-reported outcomes that represented our primary outcomes, at least over the short-term, and that AIT should therefore be considered in the management of patients with allergic rhinoconjunctivitis.

Greater standardization of trial designs and reporting techniques – in particular, in relation to choice of outcomes and their reporting so as to facilitate evidence syntheses and key subgroup analyses, would greatly help to advance the research base underpinning AIT. We therefore appreciate initiatives of the EAACI in e.g. harmonizing and standardizing clinical endpoints in AIT (187) or determining threshold-level of relevant pollen seasons for assessing clinical effect sizes. (188) We also wish to highlight the need for additional studies focusing on long-term outcomes and on studies of ILIT and other novel modes of delivery. We hope that future researchers will build on the findings from this systematic review and aim to fill key evidence gaps and areas of continuing uncertainty.

The findings from this review will be used to inform the development of recommendations for EAACI's Guidelines on AIT for Allergic Rhinoconjunctivitis.

Conclusions

AIT is effective in achieving clinically important short-term improvements in symptom, medication and combined symptom and medication scores. There is a limited body of evidence on the longer-term effectiveness of AIT in improving symptom scores.

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Online supplement

Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis

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METHODS

The methods have been reported in detail in our published protocol (12).

Search strategy

A highly sensitive search strategy was developed and validated study design filters were applied to search electronic bibliographic databases. To retrieve randomized controlled trials (RCTs), we applied the Cochrane highly sensitive search strategy for identifying RCTs in MEDLINE.(16) We searched the following databases: Cochrane Library including, Cochrane Database of Systematic Reviews (CDSR), Database of Reviews of Effectiveness (DARE), CENTRAL (Trials), Methods Studies, Health Technology Assessments (HTA), Economic Evaluations Database (EED), MEDLINE (OVID), Embase (OVID), CINAHL (Ebscohost), ISI Web of Science (Thomson Web of Knowledge), TRIP Database (www.tripdatabase.com), Clinicaltrials.gov (NIH web), Clinical Trials Register (www.clinicaltrialsregister.eu) launched by the European Medicines Agency (EMA), Current controlled trials (www.controlled-trials.com), Australian and New Zealand Clinical Trials Registry (http://www.anzctr.org.au). To retrieve case series, we used the filter developed by librarians at Clinical Evidence: http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html

The search strategy was developed on OVID MEDLINE and then adapted for the other databases. In all cases, the databases were searched from inception to October 31, 2015.

Subgroup analyses

Subgroup analyses were undertaken to compare:

- Children <18 years versus adults ≥18 years; (this represented a change from our plans to compare young children versus adolescents versus adults, which was necessitated by data not being available in formats suitable to support the original planned subgroup analyses)
- SCIT versus SLIT
- AIT for seasonal versus perennial allergens
- Modified allergen extracts (allergoids) versus unmodified allergen extracts in SCIT
- Pre-seasonal (short term treatment) versus continuous treatment in SCIT

- Pre-/co-seasonal (short term treatment) versus continuous treatment in SLIT
- Aqueous solutions versus tablets in SLIT.

RESULTS

Effectiveness

Description of trials

We identified 61 SCIT RCTs (reported in 63 papers) (19–81) including 6,379 patients, 71 SLIT RCTs (reported in 75 papers)) (82–119,119–121,121–156) including 13,636 patients and two ILIT RCTs (157,158) including 56 patients (Tables 1a-c). The overwhelming majority of trials only reported on short-term effectiveness (Tables 2a-c).

SCIT

The majority of trials were led by teams from the UK (n=11), followed by: France (n=7); Spain (n=7); Italy (n=6); Germany (n=5); USA (n=5); Canada (n=3); Poland (n=4); Denmark (n=2); Sweden (n=2); Germany and Austria (n=2); Austria, Denmark, France, Italy, Sweden (n=1); Austria, Spain, Germany, (n=1); Australia, Canada, UK and USA (n=1); Belgium and the Netherlands (n=1); India (n=1); Sweden and Germany (n=1), and Macedonia (n=1).

The majority of studies included adult participants (n=42). Fifteen studies included participants of any age (i.e. children and adults) and one included children aged up to 18 years of age. Three studies did not report the age of the participants.

The most common allergen administered in the included studies was: grass pollen(s) (n=28), followed by: weed pollens (n=19); tree pollens (n=16); HDM (n=6); molds (n=3); cat dander (n=2); dog dander (n=1); and storage mites (n=1).

SCIT was performed with a single allergen (i.e. allergens from the same group e,g, grasses) in 55 studies and with multiple allergens (i.e. from different groups e.g. grass and tree pollens) in the remaining six studies. In these trials, SCIT was compared with placebo (n=53), routine care (n=4) or active treatment (n=12); (there was more than one comparator arm in some studies).

SCIT was administered continuously in 27 studies, pre-seasonally in 19 studies, pre- and co-seasonally in 11 studies, pre-seasonally and continuously in different arms in one study and co-seasonally in one trial. The remaining trials (n=2) did not report on timing of administration.

The protocols used were: conventional (n=45); cluster (n=9); rush (n=8); semi-rush (n=1); and ultra-rush (n=1). Two studies uses both conventional and cluster, and a further study used both rush and conventional protocols.

The duration of treatment was heterogeneous, ranging from a single injection to four years. It was unclearly reported in one study and not reported at all in another trial.

Short-term effectiveness of SCIT was assessed by symptom scores (n=51), medication scores (n=46) and combined symptom and medication scores (n=20). Long-term effectiveness of SCIT was assessed by symptom scores (n=1) and medication scores (n=1), and combined symptom and medication scores (n=1).

See Tables 1a and 2a for further details.

SLIT

The majority of studies were carried out in: multiple European countries (n=16); Italy (n=12); Germany (n=7); France (n=6); Poland (n=4); US (n=3); Spain (n=3); the Netherlands (n=3); Austria (n=2); Canada (n=2); UK (n=2); Austria, Canada, Denmark, France and Germany (n=1); Brazil and the US (n=1); Canada and the US (n=1); China (n=1); Cyprus, Turkey and the UK (n=1); Czech Republic (n=1); Finland (n=1); Iran (n=1); Japan (n=1); South Africa (n=1); and Turkey (n=1).

The majority of studies were in adults (n=28), followed by children up to the age of 18 (n=25) and studies conducted in both adults and children (n=17), one study did not report the age of the participants.(40)

The major allergen type used in the immunotherapy was: was grass pollen(s) (n=40), followed by: HDM(s) (n=15); weed pollens (n=7); tree pollens (n=4); molds (n=3); and cat dander (n=2).

SLIT was performed with a single allergen in 67 studies and with multiple allergens in four studies. It was most commonly administered in the form of drops/solution (n=46), followed by tablets (n=22) and spray (n=1); the mode of administration was not reported in two studies. In relation to the drops/solution and tablet preparations, the SLIT was subsequently swallowed in 50 studies, expectorated in three studies and not reported in 18 studies.

SLIT was compared with placebo (n=67); routine care (n=1); or active treatment (n=5) (with some studies including more than one comparator).

SLIT was administered preseasonal and co-seasonally in 22 studies, pre-seasonally in seven studies and co-seasonally in five studies. The remaining studies did not report on the season of administration.

The duration of treatment varied from 28 days to four years.

Short-term effectiveness was assessed by symptom scores (n=56), medication scores (n=44); and combined symptom and medication scores (n=9). Long-term effectiveness was assessed by symptom scores (n=4), medication scores (n=2) and combined symptom and medication scores (n=2).

See Tables 1b and 2b for further details.

ILIT

The two ILIT trials were conducted in Switzerland and Sweden. They both investigated single allergen therapy, delivered through a cluster protocol to cat, and grass or birch pollen versus placebo. One used a pre-seasonal administration and the other continuous.

Both trials reported on the short-term effectiveness by symptom scores and one reported on medication scores.

See Tables 1c and 2c for further details.

Primary outcomes

Data on primary outcomes are summarized in Tables 4a-c .

Symptom scores

Long-term effectiveness

In order to investigate long-term effectiveness, a number of investigators studied a discontinuation period following trials that involved randomization to AIT or placebo in which the superiority of AIT was confirmed. In this longer-term phase, patients were followed-up and outcomes were then again assessed at least one year post-discontinuation of AIT.

There were four trials that studied this outcome, one SCIT and three SLIT, all of which were judged to be at low ROB. Meta-analysis of data was not possible. We therefore provide a descriptive summary of the main findings.

A trial by Durham (1999) studied discontinuation of SCIT in grass pollen allergic patients.(42) Participants had previously participated in a one year RCT in which they were randomized to SCIT or placebo, which confirmed the superiority of SCIT. (42) All patients were then given SCIT for three years (i.e. four years in total for the trial intervention arm). They were then randomized to receive either maintenance grass pollen SCIT or placebo injections for an additional three years. The authors found no significant difference in symptom scores between the two groups and concluded that the initial three/four years of AIT had induced prolonged clinical remission.

A five year double blind placebo controlled RCT by Durham (2012) had a three year SLIT tablets or placebo treatment period in grass pollen allergic patients followed by a two year blinded observation period when no active treatment was administered.(114) Two years after discontinuing treatment, the group who had received SLIT were found to have a significant improvement in symptom scores when compared to placebo ($P<0.004$).

Bergmann (2013) followed patients for one year after discontinuing one year of HDM SLIT at two different doses (300 IR or 500 IR) compared with placebo, which found that the active treatments significantly improved symptom scores.(89) One year after discontinuing AIT, the symptom improvements in the SLIT arms were maintained when compared to placebo.

Ott (2009) conducted a four year study which randomized patients to three years of seasonal grass pollen SLIT or placebo, followed by a one year discontinuation phase.(133) They found that improvements in symptom scores were maintained in the SLIT group after treatment was discontinued ($P=0.015$).

In summary, all four trials at low ROB found a beneficial effect on the long-term effectiveness of AIT on symptom scores.

Sensitivity and subgroup analyses and assessment of publication bias

These analyses were not possible.

Medication scores

Long-term effectivenss

There were three low ROB trials that assessed this outcome: one SCIT and two SLIT. These three trials are all described in more detail above when discussing long-term effects on symptom scores.

The trial by Durham (1999) in grass pollen allergic patients found that in the discontinuation RCT there was no significant difference between patients who continued SCIT when compared to those who received placebo.(42)

Another trial by Durham (2012) found that two years after discontinuing SLIT there was no difference in medication scores between those who had previously received SLIT compared to those who received placebo.(114)

Ott (2009) found that one year after completion of a trial of three years of seasonal grass pollen SLIT or placebo there was no significant improvement in medication scores (P=0.84).(133)

Overall, one trial found a benefit of AIT (SCIT) on long-term medication scores; the two other SLIT trials did not show a sustained effect.

Combined symptom and medication scores

Long-term effectiveness

We found one SCIT trial and two SLIT trials that reported on this outcome.

The trial by James (2011), at low ROB, studied grass allergic patients who were randomized to two years of SCIT or placebo.(53) They were randomized to receive SCIT or placebo injections during the initial trial, which found a benefit from SCIT. Those in the active arm were then randomized to a further two years of SCIT or placebo and this found low combined symptom and medication scores in both arms, similar to the scores at the end of the initial trial. The authors concluded that clinical tolerance was maintained for at least two years after discontinuation of AIT.

Ott (2009; described above), at low ROB, failed to find a significant difference in long-term combined symptom and medication scores following discontinuation of SLIT grass pollen treatment (P=0.052).(133)

Didier (2013) conducted a four year study, at unclear ROB, in which they randomized grass pollen allergic patients to SLIT commencing either four months pre-seasonally or two months pre-seasonally (i.e. two active groups) or placebo for three consecutive seasons.(109) This showed that both active treatment arms were beneficial in improving combined symptom and medication scores. They then continued to monitor patients for an additional fourth year (during which they did not receive SLIT or placebo), which found that the average adjusted symptom score (i.e. combined rhinoconjunctivitis symptom and medication score) was significantly improved in the SLIT groups when compared to placebo (two months pre-seasonal: P=0.0019; four months pre-seasonal: P=0.01) A further post-hoc analysis of this trial, was conducted at year five – i.e. two years after discontinuing AIT – and significant improvement was demonstrated in the four months group compared to placebo (P=0.047), but not in the two month preseasonal group.(159)

Overall, one of the three trials found evidence of a sustained beneficial effect on combined symptom and medication scores. The one trial at an unclear ROB (Didier 2013/2015) demonstrated a two year carry over effect of AIT in the active SLIT group that received AIT four months pre-seasonally for three consecutive seasons but not for the group which received AIT two months pre-seasonally.

Scondary outcomes

Allergen challenge models in AIT

The data for these outcomes were not reported in a format suitable for undertaking meta-analysis. We therefore provide a narrative description below with a focus on those trials judged to be at low risk of bias (ROB).

Environmental exposure chamber

Four studies were conducted with the use of an Allergen Exposure Challenge (AEC): one using SCIT and three SLIT. Two were for cat allergy one for grass pollen and one for birch pollen.

The SCIT study by Patel (2012) was judged to be at low ROB.(65) This exposed cat allergic patients to allergen at baseline and at 22 weeks and 52 weeks after treatment with a short course of FelD1-derived peptide antigen SCIT (CatPad) using two different dosing regimens (8x3nmol or 4x6 nmol). Each assessment was undertaken over four consecutive days with three hours exposure to allergen in the EEC. Total rhinoconjunctivitis symptom scores (TRSS) were measured at these assessments. At the assessment at 50-54 weeks, the higher dose (4x6 nmol) treated patients had a significantly improved TRSS score compared to placebo (P=0.01), but the lower dose group did not (P=0.74).

The high ROB SLIT study with natural cat extract by Alvarez Cuesta (2007) involved a natural exposure challenge (NCT) to cat allergen in a cat room before and after treatment.(83) There was a significant improvement with SLIT compared to placebo (P<0.001). The remaining two SLIT studies used the Vienna Challenge Chamber (VCC). The SLIT study by Horak 1998 for birch pollen administered AIT for 28 days followed by a three-month maintenance period VCC measurements of nasal air flow were taken at baseline and at the end of the maintenance period which demonstrated a significant improvement in the active group. (P=0.03)(120) The Horak 2009 study of 5 grass pollen SLIT showed the active group had a significantly lower average rhinoconjunctivitis symptom score than the placebo group after four months of treatment (P=0.0003)(121)

All of these studies thus demonstrate the effectiveness of AIT in an environmental exposure chamber.

Nasal challenge

Twenty-six studies performed nasal allergen challenge tests, 15 SCIT (23,24,27,29,30,33,37,43,52,57–59,63,64,75) and 11 SLIT (Table 1a).(84,86,87,92,93,122,128,136,139,146,150).

SCIT trials

Of the 15 SCIT studies, eight showed a significant improvement in the SCIT group compared to placebo (24,27,29,37,43,52,58,75) and four showed no significant difference between the active and control groups. (23,33,57,59) The remaining three studies did not report a between group comparison, but both reported an improvement in the active group with a higher threshold of reactivity to allergen and no such change in the control group.(63,64,160)

Nine SCIT studies were at low ROB; of these four showed no significant difference between SCIT and control groups (23,33,57,59) and three studies showed a significant difference between active and control groups. (29,37,43) The remaining two studies did not report a between group comparison, but both reported a higher allergen threshold of reactivity in the active group and no such improvement in the control group.(63,64)

SLIT trials

Eleven SLIT studies reported on this outcome of which three studies showed no significant difference between active and control groups (87,128,146) and five studies showed a significant reduction in nasal reactivity in the SLIT group compared to controls.(86,93,122,139,150) Of the remaining three studies, two reported no between group data (92,136) and the other had two active groups: the single allergen SLIT group had a significant difference between placebo in nasal reactivity, but this was not the case for the multiple allergen SLIT group.(84)

Of these, three SLIT studies were at low ROB with variying conclusions. The Amar (2009) study showed a significant improvement in the single allergen SLIT group, but not in the multiple allergen group compared to placebo (P=0.03 and P=0.11, respectively).(84) Aydogan (2013) showed no significant

improvement in the SLIT group compared to placebo following one year of house dust mite (HDM) SLIT (P>0.05).(87) Finally, Hirsch (1997) demonstrated a significant improvement in PC40 nasal flow in the SLIT group compared to placebo (P<0.05).(122)

Nasal challenge: Overall interpretation

Due to the conflicting results from higher quality SCIT and SLIT trials it is difficult to draw any clear conclusions in relation to this outcome.

Conjunctival challenge

Conjunctival challenges were undertaken in 16 studies: SCIT (n=12) (21,23,35,38,42,45,55,62,63,70,72,77) and SLIT (n=4) (Table 1b).(120,127,138,146)

SCIT studies

Of the 12 SCIT studies that reported on this outcome, one showed graphical information only (62) and four reported no between group results.(38,63,72,112) These studies will therefore not be considered further. Of the remaining seven studies, five showed no significant improvement in conjunctival provocation tests (CPT) between active and control groups(21,23,45,55,70) and two showed an improvement.(35,77)

Concentrating on the five low ROB SCIT studies, four studies showed no significant improvement in CPT in the SCIT group compared to control (21,23,45,70) whereas one demonstrated an improvement.(77)

SLIT studies

Four SLIT studies reported on this outcome: two were at high ROB (127,146) and two at an unclear ROB.(120,138) Two studies demonstrated a significant improvement in CPT in the SLIT group compared to placebo (127,138) one reported no significant improvement(146) and one reported no between group comparison. (120)

Conjunctival challenge: Overall interpretation

Four SCIT studies of high quality demonstrated that AIT is not effective in improving conjunctival provocation to allergen. There were no high quality SLIT studies that reported on this outcome, which makes it difficult to draw any firm conclusions.

Cost-effectiveness

Characteristics of studies

We identified 19 eligible studies that reported on health economic evaluations of SCIT and SLIT in both children and adults (Table 2).(160–178) Two of these 19 studies focused on patients who all had both allergic rhinitis and allergic asthma(177,178) and the remaining 17 focused on patients who had allergic rhinitis, some of whom also had asthma.

Three of these studies reported results solely from a societal perspective (160,161,180) with the other 16 reporting information from a health systems perspective.

Studies were based in a range of countries: Germany (n=7), Denmark (n=4), Italy (n=4), UK (n=4), Austria (n=2), Finland (n=2), France (n=2), the Netherlands (n=2), Sweden (n=2), Canada (n=1), Czech Republic (n=1), Norway (n=1) and Spain (n=1). Three studies reported results for more than one of these countries.

Seven of the studies reported results against disease specific outcome measures whilst the remaining 12 reported results based on quality adjusted life years (QALYs).

Thirteen of the studies were based on RCT data or meta-analyses of RCT data (160–169,176–178) including two model based evaluations (165,169) with the remaining studies being based on a mixture of questionnaires, observation data and expert opinion. None of the studies based on non-random data attempted to control for selection bias. None of the RCT-based studies described the amount of missing data in the study or explained how if at all any missing data were imputed for in the analyses.

Study time horizons ranged between one year and 15 years with the longer time horizon studies, of which the last were typically based on much shorter follow-up trial data (typically one year) and assuming constant continued treatment effect even after treatment was discontinued.

Nine of the studies compared SLIT versus standard care,(161,163,169,166–171,177,178) three studies compared SCIT versus standard care,(162,169,172) two studies compared AIT (undefined) versus standard care,(173,175) seven studies compared SCIT versus SLIT (160,165,167–169,174,176) and of these two studies compared different SLIT treatments.(165,167)

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AIT for allergic rhinoconjunctivitis: a systematic review and meta-analysis
Tables and figures to accompany main paper

Table 1a: Characteristics of SCIT studies (n=61 studies, reported in 63 papers)

Study (First author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol									Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Alvarez-Cuesta, 2005, Spain	X	X								X	X					X	X					1 y	Glutaraldehyde-polymerized extracts / NR (Laboratorios LETI, S.L.)	X	X					X	X
Ariano, 1999, Italy			X						X		X					X	X					1 y	Glutaraldehyde modified allergoid extract of *Parietaria judaica (50%) & Parietaria officinalis* (50%)/ Purethal®			X				X	
Arvidsson, 2002, Sweden		X							X		X						X	X				2 y	Birch depot extract adsorbed onto aluminum hydroxide / Alutard SQ ®	X	X					X	
Balda, 1998,		X							X		X			X			X					7	Purified and standardized extracts composed of equal parts of *Corylus avellana, Alnus glutinosa, and*	X	X					X	

Study (First author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Germany																						w	*Betula verrucosa* / ALK7 Frűhbltihermischűng®								
Bodtger, 2002, Denmark		X							X		X			X	X			X				1 y	*Betula verrucosa* extract / Soluprick SQ® (ALK-Abello´)	X	X					X	
Bousquet, 1987, France	X								X		X		X	X	X					X		10 m	Six-mixed grass-pollen allergoid and standardized orchard grass-pollen extract / Alyostal ST® (Stallergenes)	X	X					X	
Bousquet, 1989, France	X								X				X	X	X					X		8 m	SCIT with a high-molecular-weight formalinized allergoid (HMW-GOID) vs SCIT with unfractionated allergoid (GOID) vs SCIT with standardized extract vs placebo / NR	X	X					X	
Bousquet, 1990, France	X								X		X		X	X	X					X		NR	High-molecular weight mixed grass pollen allergoids / NR	X	X					X	
Bousquet, 1991, France	X	X	X							X	X			X						X		1 y	Standardized extracts from orchard grass (*Dactylis glomerata*), olive (*Olea europaea*), plane tree (*Platanus occidentalis*), mugwort (*Artemisia vulgaris*), and *Parietaria officinalis* pollens / NR (manifactured by Stallergenes)			X				X	

Study (First author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Bozek, 2016, Poland	X								X		X			X			X					3 y	Pollen mixture extract solution of grass pollens (*Agrostis stolonifera, A odoratum, Arrhenatherum elatius, D glomerata, Festuca rubra, Holcus lanatus, Lolium perenne, P pratense, P pratensis, Secale cereal, and Loe edasi*) / Purethal grasses (HAL Allergy BV)	X	X	X				X	X
Brunet, 1992, Canada			X						X		X			X			X					3 m	Alum-precipitated aqueous ragweed extracts / NR	X	X					X	
Ceuppens, 2009, Belgium & the Netherlands		X							X		X					X	X					18 m	Glutaraldehyde-modified birch pollen extract adsorbed onto aluminium hydroxide /PURETHAL® Birch			X				X	
Chakraborty, 2006, India		X							X		X					X	X					2 y	*Phoenix sylvestris Roxb* or sugar palm allergoid extract / NR			X				X	
Charpin, 2007, France		X							X		X					X	X					15 m	Standardized, aluminum hydroxide-adsorbed *Juniperus ashei* extract/ Alustal® (Stallergenes)	X	X					X	X
Colas, 2006,			X						X		X					X		X				1 y	Depigmented and glutaraldehyde polymerized extract of *Salsola kali* absorbed onto aluminium	X	X					X	X

Study (First author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol									Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Spain																							hydroxide/ NR (supplied by Laboratorios LETI, SL.)								
Corrigan, 2005, UK	X								X		X			X			X					2 y	Aluminium-adsorbed six-grass pollen allergoid / Allergovit®	X	X					X	X
Crimi, 2004, Italy			X						X		X					X		X				3 y	Intact *Parietaria judaica* extract adsorbed onto aluminum hydroxide / Alutard SQ®	X	X					X	
Dokic, 2005, Macedonia					X				X		X						X					3 y	Aluminium hydroxide adsorbed *D.pt.* allergoid / NR (Allergopharma)	X	X					X	
Dolz, 1996, Spain	X								X		X					X				X		3 y	Grass-pollen allergen extract (*Phleum, Dactylis, Lolium*) adsorbed onto aluminum hydroxide / Alutard SQ® (ALK-Abelló)	X	X					X	
Drachenberg, 2001, Germany and Austria	X								X		X			X			X					4-7 w	Tyrosine-adsorbed glutaraldehyde-modified grass pollen extract containing monophosphoryl lipid A as adjuvant / Pollinex Quattro ®	X	X	X				X	
Drachenberg, 2002,		X							X		X			X			X					4-7	L-tyrosine-adsorbed birch, alder, hazel pollen allergoids treated with glutaraldehyde plus			X				X	

Study (First author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Germany																						w	monophosphoryl lipid-A (MPL) / Pollinex Quattro ®								
DuBuske, 2011, USA, Canada, UK, Austria	X								X		X			X			X					4-8 w	Modified Allergen Tyosine Adsorbate (MATA) consisting of a mixture of modified pollen allergens from 13 grass species adsorbed onto tyosine/ Pollinex Quattro, Pollinex Complete; Allergy Therapeutics, U.K.			X				X	
Durham , 1999, UK Primary study Varney, 1991	X								X		X		X			X	X	X				3 y	Standardized, aluminum hydroxide–adsorbed, depot grass pollen vaccine / Alutard SQ® (ALK Abelló)				X	X		X	
Ewan , 1988, UK					X				X		X								X			3 m	Partially purified extract of *D. pteronysinus* / Pharmalgen®	X						X	
Fell, 1988, UK	X								X		X			X							X	1 injectio	Enzyme (glucuronidase) potentiated grass pollen allergens / (Pharmacia)	X	X						

Study (First author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol									Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
																						n								
Ferrer, 2005, Spain			X						X		X					X	X					20 m	Biologically standardized extract of *Parietaria judaica* adsorbed onto aluminium hydroxide gel / Pangramin ®Depot, ALK-ABELLÓ	X	X	X				X	X
Frew, 2006, UK	X								X		X		X	X	X		X					1 y	Standardized depot preparations of grass pollen extract / Alutard SQ grass pollen® (ALK-Abello´)	X	X					X	X
Grammer, 1982, USA			X						X		X	X		X			X					15 w	Polymerized ragweed extract (PRW)/NR	X						X	
Grammer, 1983, USA	X								X		X			X			X					4 m	Six grass pollen allergoid prepared by polymerization with glutaraldehyde / NR	X	X					X	
Grammer, 1984, USA			X						X		X	X		X			X					>30 m (UR)	Polymerized ragweed extract / NR			X			X	X	
Grammer,	X								X		X			X			X					4	Polymerized ragweed extract / NR			X				X	

Study (First author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol									Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
1987, USA																						m								
Höiby, 2010, Sweden & Germany		X							X		X					X	X					18 m	Depigmented polymerized birch pollen (Betula alba) extract adsorbed onto aluminium hydroxide/ Depigoid ®(Laboratorios LETI Sl)			X				X	
Horst, 1989, France				X					X		X					X				X		1 year	lyophilized and standardized Alt extract Stallergnes Laboratories			X				X	
Iliopoulos, 1991, USA			X						X		X			X	X		X					~8 m	Short ragweed extract / NR (Greer Laboratories,Lenoir, N.C.)			X				X	
James, 2011, UK	X								X		X					X	X					2/4 y	*Phleum pratense* extract adsorbed with aluminum hydroxide / Alutard SQ ®				X		X		
Juniper, 1990, Canada			X						X			X		X	X		X					6 w	Modified ragweed tyosine adsorbate / Pollinex® (Bencard Allergy Service)	X	X					X	
Jutel, 2005, Poland	X								X		X			X	X		X					8-9 m	Five recombinant grass pollen allergens / NR (Allergopharma)			X				X	X

Study (First author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol												Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Kleine-Tebbe, 2014, Spain, Germany & Austria	X								X		X		X			X	X					1 y	Aluminium hydroxide adsorbed Phleum pratense extract / AVANZ ® Phleum pratense (ALK)	X	X					X	
Klimek, 2014, Germany	X		X							X	X			X	X			X				1 y	Glutaraldehyde-modified high polymerized allergen extract containing 6 grasses (60%) and rye pollen adsorbed onto aluminum hydroxide / CLUSTOID® (ROXALL Medizin)	X	X	X				X	
Kuna, 2011, Poland				X					X		X					X	X					3 y	*Alternaria alternata* extract in a depot formulation with aluminum hydroxide / Novo-Helisen Depot ® A alternata 100% (Allergopharma)	X	X	X				X	X
Leynadier, 2001, France	X								X		X					X	X					1 y	Standardized five-grass-pollen (equal parts of: orchard, meadow, rye, sweet vernal and timothy) depot extract adsorbed onto calcium phosphate / Phostal® (Stallergenes)	X	X	X				X	
Metzger, 1981, England			X						X		X			X			X					5 w	Glutaraldehyde-modified, tyosine-adsorbed short ragweed extract / NR (Beecham Laboratories)	X						X	

Study (First author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Mirone , 2004, Italy			X						X		X					X	X					1y (DBRCT)	*Ambrosia artemisiifolia* absorbed onto aluminium hydroxide and suspended in phenolated (0.4% w/v) saline solution / NR (ALK-Abello`)	X	X					X	
Olsen, 1995, Denmark	X	X	X							X			X			X	X					2 y	Aluminium hydroxide adsorbed extracts of standardized extracts of *Betula, Phleum and Artemisia* / Alutard® SQ (ALK)	X						X	
Ortolani, 1994, Italy			X						X		X					X	X					1 y	Partially purified alginate-conjugated extract of *Parietaria judaica* / Conjuvac Parietaria ® (Dome Hollister-Stier)			X				X	
Pastorello, 1992, Italy	X								X		X			X	X		X					5-12 m	Formalinized depot 6 grass allergoid absorbed onto aluminum hydroxide / NR (Allergopharma)			X				X	
Patel, 2012, Canada						X			X		X		X					X				3 m	Fel d 1–derived peptide antigen (Cat-PAD) / NR (Bachem and Patheon)	X*			X*			X	

Study (First author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Pauli, 2008, Austria, Denmark, France, Italy & Sweden		X							X		X		X			X	X					2 y	Aluminum hydroxide–adsorbed vaccines of birch pollen extract, *rBet v 1*, and *nBet v 1* / NR (Stallergenes SA)	X	X					X	
Pfaar, 2010, Lithuania, Poland & Germany		X							X		X					X	X					19 m	Standardized depigmented and glutaraldehyde-polymerized tree pollen extract (33% *Corylus avellana*, 33% *Alnus glutinosa*, 34% *Betula alba*) adsorbed onto aluminium hydroxide / Depigoid(Laboratorios LETI SL, Tres Cantos, Spain),	X		X				X	
Pfaar, 2011, Germany	X								X		X			X						X		2 y	Depigmented and glutaraldehyde-polymerized grass pollen mix adsorbed onto aluminum hydroxide / Depiquick® (Laboratorios LETI)	X	X	X				X	X
Powell, 2007, UK Primary study Frew, 2006	X								X		X		X			X	X					14 m	Standardized depot preparations of grass pollen extract / Alutard® SQ grass pollen (ALK-Abello´)								X

Study (First author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol										Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Radcliffe , 2003, UK	X	X	X	X	X	X	X	X		X	X			X								2-3 m	Enzyme potentiated mixed inhaled allergen extract (pollen mixes for trees, grasses, and weeds; allergenic fungal spores; cat and dog danders; dust and storage mites) / NR	X						X	X
Rak, 2001, Sweden		X							X			X		X				X				1 y	Birch pollen extract adsorbed onto aluminum / Alutard® (ALK-Abelló)	X	X						
Riechelmann , 2010, Germany & Austria					X				X		X					X	X					1 y	Single-strength glutaraldehyde-modified aluminum hydroxide–adsorbed extract / HDM PURETHAL Mites ® (HAL-Allergy)	X	X					X	X
Tabar, 2005, Spain					X				X				X				X	X				1 y	Biologically standardized HDM depot extract adsorbed on aluminum hydroxide / Pangramin Depot UM D pteronysinus® (ALK-Abello´)	X	X					X	
Tabar, 2008, Spain				X					X		X					X	X					18 m	Metabolic extract of *Alternaria alternata* / Allergovac® depot	X	X					X	X
Tari, 1997, Italy			X						X		X					X	X					2 y	Alum-adsorbed *Parietaria judaica* pollen allergoid/ Allergovit® (Allergopharma)	X	X					X	

Study (First author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol											Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Tworek, 2013, Poland	X		X							X			X	X		X	X					3 y	Allergoid preparation consisting of 80% grass pollen and 20% rye pollen extracts / Allergovit® (Allergopharma)	X	X	X				X	
Varney, 1991, UK		X							X		X			X	X		X					8 m	Partially purified and standardised extract of *Phleum pratense* adsorbed onto aluminium / Alutard SQ® (ALK-Abelló)	X	X					X	
Varney, 2003, UK					X				X							X	X					1 y	Intact HDM extract vaccine adsorbed onto aluminum hydroxide/ Alutard SQ® (ALK-Abelló)	X	X					X	
Walker, 2001, UK	X								X		X					X		X				2 y	Alutard SQ (ALK Abelló, Horshølm, Denmark), a standardized extract of Phleum pratense (timothy grass pollen),7 aluminum adsorbed for slow release	X	X					X	X
Weyer, 1981, France	X								X		X			X			X					8 m	Crude 4 grass pollen extract / NR	X	X	X				X	

Study (First author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol									Short-term effectiveness			Long-term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	Single	Multiple	Placebo	Routine care	Active	Pre-seasonal	Co-seasonal	Continuous	Conventional	Cluster	Semi-rush	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Zenner, 1997, Germany	X		X						X		X				X		X					4 m	Partially purified and standardized extracts of 6 grasses (50%, *Dactylis glomerata, Lolium perenne, Arena elatior, Phleum pratense, Poa pratensis, and Fetuca pratensis*) and rye, (50%, *Secale cereale*) adsorbed onto aluminum hydroxide / NR (manufactured by ALK A/S)	X	X					X	

***AIT**, allergen specific immunotherapy; **m,** month; **NBS**, not better specified; **NR**, not reported; **Rx,** treatment; **SCIT**,* subcutaneous immunotherapy; ***SLIT**, sublingual immunotherapy; **UR,** unclear reporting **w,** week; **y**, y.*

**environmental exposure chamber*

Table 1b: Characteristics of SLIT studies (n=71 studies, reported in 75 papers)

udy (First author, y, country)	Allergen(s) type								Allergen no.		Comparator			AIT Protocol									Short term effectiveness			Long term effectiveness			Safety	Quality of life
	Grass pollen(s)	Tree pollen(s)	Weed(s)	Mold(s)	House dust mite	Cat	Dog	Other(s)	[illegible]	Mixed	Placebo	Routine care	Active	Pre-seasonal	[illegible]	Continuous	Conventional	[illegible]	[illegible]	Rush	Ultra-rush	Rx duration	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Symptom score	Medication score	Combined score		
Ahmadiafshar, 2012, Iran	X								X		X			X	X						X	6 m	10, 100, and 300 IR rye grass spray (Staloral 638)	X	X					X	
Alvarez-Cuesta, 2007, Spain						X			X		X											12 m	Aqueous solution of cat dander extract with NaCl 0.9%, phenol 0.4% and glycerol 50% (protocol supplied by Laboratorios LETI, S.L.	X						X	
Amar, 2009, US	X									X	X		X			X						10 m	Monotherapy group: timothy extract Multiple allergen group: same amount of timothy plus 1 mL each of an additional 9 unstandardized extracts 1:20 wt/vol in 50% glycerin: maple, ash, juniper, American elm, cottonwood, Kochia, ragweed, sagebrush, and Russian thistle (ALK-Abello´).	X	X					X	
André, 2003, France			X						X		X				X							6.5 m	standardized ragweed extract (Stallergènes SA, Antony, France)	X	X					X	
Ariano, 2001, Italy & France		X							X		X					X						12 m	Aqueous solution of an allergic fraction of *Cupressus arizonica* partially purified through dialyis in a phyiological solution with 15% glycerin.	X	X					X	
Aydogan, 2013, Turkey, UK & Cyprus.					X				X		X											12 m	1:1 mixture of *D. pteronysinus and D. farinae* (STALORAL, Stallergenes SA, Antony, France)	X	X						
Bahçeciler, 2007, Turkey					X				X		X											6 m	*D. pteronysinus and D. farinea* 50/50 extract.	X							
Bergmann, 2013, Germany, France, the Netherlands & Spain					X				X		X											2 y	Oral tablets of 1:1 mixture of *D pteronysinus and D farinae* (28 mg and 120 mg respectively for the 500 IR tablet, 16 mg and 68 mg respectively for the 300 IR tablet)	X			X			X	
Blaiss, 2010, US & Canada	X								X		X											18 m	f 2,800 bioequivalent allergen units of grass AIT treatment (oral lyophilisate, *Phleum pratense*, 75,000 standardized quality tablet, containing approximately 15 mg of Phl p 5; Schering-Plough Corp, a division of Merck & Co, Kenilworth, NJ)	X	X	X				X	X
Bowen, 2004,			X						X		X			X								4	Ragweed allergen extract	X	X					X	

Canada																				m										
Bozek, 2012, Poland					X				X		X									3 y	Oral Staloral 300 SR Der p and Der f (1:1)	X	X					X	
Bozek, 2014, Poland	X								X		X									3 y	Oral Staloral 300 SR 5 grass pollen solution *of P. pratense, D. glomerata, A. odoratum, L. perenne, and P. pratensis* (Stallergenes)	X	X					X	
Bufe, 2004, Germany	X								X		X			X						3 y	Grass pollen extracts (Sublivac B.E.S.T.TM, HAL-Allergy, Haarlem, the Netherland)								
Bufe, 2009, Germany	X								X		X			X	X					8-23 w	Orodispersible, fast-dissolving, SQ-standardized grass allergen tablet (Grazax; ALK, Hørsholm, Denmark; 75,000 SQ-T/2800 bioequivalent allergen units, approximately 15 mg Phl p 5, Phleum pratense major allergen 5)	X	X					X	
Caffarelli, 2000, Italy	X								X		X			X						3 m	Mixture of monomeric grass-pollen allergens (33% *Holcus lanatus*, 33% *Phleum pratense*, and 33% *Poa pratensis*) in tablets (LAIS, Lofarma S.p.A, Milan, Italy)	X	X					X	
Clavel, 1998, France	X								X		X									7 m	Mixture of five major grass pollens (orchard grass, meadow grass, ryegrass, sweet vernal grass, and timothy grass	X	X					X	
Cortellini, 2010, Italy				X					X		X									10 m	Glycerinated *Alternaria alternata* extract in droplets (Anallergo, Firenze, Italy)	X	X					X	
Cox, 2012, US	X								X		X									6 m	300IR SLIT tablets containing a standardized 5-grass pollen allergen obtained by means of extraction of a mixture of 5 grass pollens in equal amounts (orchard grass, *Dactylis glomerata*; Kentucky bluegrass, *Poa pratensis*; perennial rye grass, *Lolium perenne*; sweet vernal grass, *Anthoxanthum odoratum*; and timothy grass, *Phleum pratense*)	X	X	X				X	X
Creticos, 2013, US			X						X		X			X	X					20 m	Short ragweed tablets (1.5, 6, or 12 units of *Ambrosia artemisiifolia* major allergen 1 [Amb a 1-U])	X	X	X				X	
Creticos, 2013, Canada			X						X		X				X					12 w	ragweed SAIL (RW-SAIL) Standardized glycerinated short ragweed	X		X				X	
Dahl, 2006, Denmark, Germany, Italy, the Netherlands, Sweden, Austria, Spain & UK	X								X		X			X	X					1 y	Grass pollen allergen tablet (GRAZAX) (75,000 SQ-T; 15 mg major allergen *Phleum p* 5)	X	X					X	
Dahl, 2006, Denmark & Sweden	X								X		X			X	X						Orodispersible grass allergen tablet (GRAZAX; approximately 15 mg major allergen *Phleum pretense* (75 000 SQ-T)	X	X					X	
de Blay, 2007, France	X								X		X			X	X					12 m	3-grass pollen extract (33.3% *Dactylis glomerata* [orchard grass], 33.3% *Phleum pretense* timothy grass], and 33.3% *Lolium perenne* [rye grass]) Allerbio, Varennes-en-Argonne, France) in 50% glycerin	X	X					X	X

De Bot, 2011, The Netherlands					X				X		X									2 years	aqueous extract of house dust mites (*D pter*,) in a glycerinated isotonic phosphate-buffered solution (Oralgen Mijten) / placebo treatment consisting of the glycerol-containing solvent	X	X					X	X
Demoly, 2015, Europe					X				X		X									1 y	1:1 mixture of two species of house dust mite allergens (*D. pteronysinus and D. farinae*) (1:1:1:1 ratio of the major allergens *Der p 1, Der f 1, Der p 2*, and *Der f 2*)	X	X					X	X
Didier, 2007, Europe	X								X		X			X	X					6 m	Mixture of 5 grass pollens (orchard, meadow, perennial rye, sweet vernal, and timothy grasses)	X						X	X
Didler, 2009, France, Germany & Spain	X								X		X		X	X	X					6 m	Lyophilized vaccines of five grass pollens (orchard or cocksfoot (*Dactylis glomerata*), meadow (*Poa pratensis*), perennial rye (*Lolium perenne*), sweet vernal (*Anthoxanthum odoratum*) and timothy *(Phleum pratense))*	X						X	
Didier, 2013, Denmark, Austria, France, Canada & Germany	X								X		X			X	X					4 y	300IR tablets containing mixture of 5 grasses [cocksfoot (*Dactylis glomerata*), meadow (*Poa pratensis*), rye (*Lolium perenne*), sweet vernal (*Anthoxanthum odoratum*) and timothy (*Phleum pretense)*	X						X	X
Durham, 2005, Canada, Denmark & Sweden	X								X		X			X	X					2 y	Fast-dissolving grass allergen tablet (ALK-Abello A/S) containing timothy grass extract (*Phleum pratense)*	X	X					X	X
Durham, 2007, UK Primary study: Dahl, 2006	X								X		X									16 w	Grass allergen tablet (Grazax)								
Durham, 2009, UK Results after 1 y follow-up of Dahl, 2006 study	X								X		X			X	X					3 y	Grass allergen tablet with *Phleum pratense* 75,000 SQ-T/2,800 BAU (ALK-Abello´, Hørsholm, Denmark) (Grazax)								
Durham, 2011, UK Results of 2 y follow-up of Dahl 2006 trial	X								X		X								X	2 y	SQ-standardized grass allergy tablet (*Phleum pratense* 75 000 SQ-T/2,800 BAU, ALK, Denmark) (Grazax)						X		
Durham., 2012, UK, Austria, Germany, the Netherlands, Sweden & Denmark Results of 2 y follow-up of Dahl 2006 trial	X								X		X			X	X					3 y	SQ-standardized grass allergy tablet (Grazax)				X			X	
Drachenberg, 2002, Germany	X	X								X	X					X					Grass, rye or birch pollens	X	X	X					
Feliziani, 1995, Italy	X								X		X			X	X			X			Grass pollen extracts (5 x 1 drop of 0.04 BU/ml, up until 5 x 1 drop of 100 BU/ml)	X	X					X	
Frølund, 2010, Austria, Denmark & UK	X								X		X			X	X					4 y	SQ-standardized grass allergy immunotherapy tablet (AIT), Grazax (*Phleum pratense* 75,000 SQ-T/2800 BAU; ALK, Denmark).								X
Guez, 2000,					X				X		X									24	*D. pteronysinus and D. farinae*	X	X					X	

France																						m	50/50 extract								
Halken, 2010, Germany, Denmark, Poland, France & Spain	X							X		X			X	X								10 m	five-grass pollen 300IR tablets (Stallergènes SA, France)	X						X	
Hirsch, 1997, Germany					X			X		X												12 m	Purified *D. pteronysinus* extract in 50% aqueous glycerol (cumulative dose 570 jag) (Allergopharma J. Ganzer KG, Reinhek, FRG)	X	X						
Horak, 1998, Austria		X						X		X												4m	Biologically standardized *Betula Alba* Alergia e Immunologia Abello SA	X						X	
Horak, 2009, Austria	X							X		X												4m	300-IR 5 grass pollen tablet (orchard, meadow, perennial rye, sweet vernal, timothy)	X						X	
Hordijk, 1998, the Netherlands	X							X		X				X								10 m	Glycerinated (50% w/v) five-grass pollen extract (*Anthoxanthum odoratum* (Sweet vernal grass), *Cynodon dactylon* (Bermuda grass), *Dactylis glomerata* (Orchard grass), *Holcus lanatus* (Velvet grass) and *Phleum pratense* (Timothy grass)) (9,500 BU/ml) (Oralgen) (ARTU Biologicals Europe B.V., Lelytad, The Netherlands)	X						X	
Ibanez, 2007, Spain & Germany	X							X														28 d	Orodispersible grass allergen tablet (75,000 SQ-T; 15 Ig *P. pratense* major allergen (Phl p 5)) (Grazax) ALK-Abello A/S, Horsholm, Denmark)							X	
Ippoliti, 2003, Italy					X			X		X												6 m	*D. pteronysinus* extract	X							
Kaluzinska-Parzyzek , 2011, Poland (Polish, translated)	X							X		X			X	X			X					2 y	Staloral 300 IR (Stallergenes)								
La Rosa, 1999, Italy & France			X					X		X												2 y	*P judaica* extract (Stallergènes, Antony, France) in drops	X	X					X	
Marcucci, 2003, Italy					X			X		X												1 y	house dust mite allergens (1 ml of the top-dose vial 1000 STU/ml/4 lg of the major mite allergen Group 1 and 2 lg of the major mite allergen Group 2)								
Moreno-Ancillo, 2007, Spain	X								X	X			X	X								10 m	2 µg of grass Group 5 and 3 µg of Olive europaea Ole e 1 (daily)	X	X	X				X	X
Mosbech., 2014, Denmark, Italy, Germany & France					X			X		X												1 y	Oral lyophilisates containing *D. pteronysinus* and *D. farinae* in a 1:1 ratio . Three active strengths were investigated: 1, 3, and 6 SQ-HDM.			X				X	X
Mosges, 2007, Germany	X								X	X												9 m	Grass and rye pollen extract mixture solution (Staloral(r) (Stallergenes, Antony, France)) and a tablet (freeze-dried pollen extract)		X	X				X	
Okubo, 2008, Japan		X						X		X			X	X		X						7 m	Diluted cedar antigen extract (2 to 2000 JAU/ml)		X					X	X
Ott, 2009, Germany	X							X		X				X							X	3 y	Pollen extract mixture of five grasses (cocksfoot or orchard, meadow, perennialrye, sweet vernal and timothy grasses; Staloral, Stallergenes SA,France) (300 IR/ml, equivalent to 21	X	X	X	X	X	X	X	

																					lg/ml of Phleum pratense major allergen)								
Nelson, 1993, US						X			X		X										10 5 d	Cat dander extract (total dose: 4.5 AU)	X						X	
Pajno, 2003, Italy			X						X		X	X	X	X	X						14 m	*P. judaica*, fluticasone	X	X						
Palma-Carlos, 2006, Italy	X								X		X		X	X							2 y	Mixture of carbamylated grass pollens (*Holcus lanatus* 33%, *Phleum pratense* 33%, and *Poa pratensis* 33%) in tablets	X						X	
Panzner, 2008, Czech Republic	X								X		X			X							1 y	Mixture of six grass pollen species extracts (oat grass (*Arrhenatherum elatius*), orchard grass (*Dactylis glomerata*), fescue (*Festuca sp.*), rye grass (*Lolium sp.*), timothy grass (*Phleum pratense*) and rye (*Secale cereale)*) (H-Al per os) (Sevapharma A.S., Prague, Czech Republic)	X		X					X	
Passalacqua, 1996, Italy					X				X		X										2 y	Monomeric allergoid tablets with *Dermatophagoides pteronysinus and D farina*	X						X	
Passalacqua, 1999, Italy	X								X		X			X						X	7 m	ALK-Abello (major allergen Par j) (0.016, 0.08, 0.4, 2, and 10 BU/mL)	X	X					X	
Passalacqua, 2006, Italy					X				X		X				X						2 y	Monomeric carbamylated grass pollen allergen (Lais)	X	X					X	X
Pfaar, 2008, Germany, Poland & Macedonia	X								X		X										2 y	Six-grass pollen mixture (high-dose)	X						X	
Pradalier, 1999, France	X								X		X										4.5 m	Five-grass-pollen extracts (orchard grass, meadow grass, ryegrass, sweet vernal grass, and timothy grass) (Stallerge Ánes SA, Antony, France)	X	X					X	
Purello-D'Ambrosio, 1999, Italy			X						X		X			X						X	6 m	*P. judaica* extract (five 3-ml vials: 0.016 BU/ml (vial 0), 0.08 (#1), 0.04 (#2), 2.00 (#3), and 10.00 (#4) in phyiologic saline with 50% v/v of glycerol & 0.4% w/v of phenol) (maximum concentration of major allergen Par j 1: 0.6 mg/ml)	X	X					X	
Queiros, 2013, Brazil & US					X				X		X		X								18 m	SLIT 1:*D. pteronysinus* extract (FDA Allergenic Ltda, Rio de Janeiro, Brazil) SLIT 2: *Dpt plus* mixed respiratory bacterial (MRB) (FDA Allergenic Ltda)			X				X	
Rak, 2006, UK	X								X		X										17 4 d	Grass pollen allergen tablets (2,500, 25,000, and 75,000 SQ-T)								X
Roder, 2007, The Netherlands	X								X		X				X						2 yea rs	Aqueous extracts of 5 grass pollen (*Lollium perenne, Phleu*m pratense, Dactylis glomeratein, Anthoxantum odoratum, Holcus lanatus) Oralgen grass pollen, Artu Biologicals	X	X					X	X
Rolinck-Werninghaus, 2004, Germany	X								X		X				X X						32 m	Pangramin (0.5 lg major allergens) (ALK-SCHERAX) three times weekly	X	X					X	
Sabbah, 1994, France	X								X		X										4 m	Five-grass pollen extracts in glycerol-saline diluent (from 1 drop of 1 IR/ml up to 20 drops of 100 IR/ml)	X	X					X	
Stelmach, 2011, Poland	X								X		X			X	X						2 y	Staloral 300 IR with five grass pollen (*Dactylis glomerata, Anthoxanthum odoratum, Lolium*	X	X					X	

																				perenne, Poa pratensis and Phleum pretense)								
Tari, 1990, Italy					X			X		X										18 m	Graded courses of aqueous mite extract with 0.4% phenol	X						X	
Valovirta, 2006, Finland		X						X		X		X								19 m	Intervention arm #1: *Betula verrucosa, Corylus avellana and Alnus glutinosa* (weekly dose: 24 000 SQ-U); intervention arm #2: *Betula verrucosa, Corylus avellana and Alnus glutinosa* (weekly dose: 200,000 SQ-U)	X	X					X	
Van Niekerk, 1987, South Africa	X							X		X										24 m	Mixture of aqueous extracts of twelve grass pollens (B2 grasses) (Bencard, UK), plus Bermuda grass pollen and maize pollen in phosphate buffered phyiological saline with 0 5% w/v phenol identical to Bencard SDV® vaccine (Beechams, UK)	X						X	
Vourdas, 1998, Greece & France		X						X		X										2 y	Olive pollen extract (major allergen Ole e 1 13.5 jig/ml (100 IR/ml)) (four concentrations: 1, 10, 100, and 300 IR/ml) (Stallergenes SA)	X	X					X	
Wang, 2013, China					X			X		X										6 m	Mixture of *D. pteronysinus and D. farinae* in 50% glycerol solution (Zhejiang Wolwo BioPharmaceutical Co., Ltd., China) (five treatment dosages with different concentrations: 0.75 lg/ml, 7.5 lg/ml, 75 lg/ml, 250 lg/ml, and 750 lg/ml)	X	X					X	
Wahn, 2012, Germany & Poland	X							X		X			X	X						8m	Aqueous grass pollen preparation containing 6 species (*Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense, and Poa pratensis*) in a water/glycerol solution with phosphate-buffered saline (40 µg per maintenance dose) Allergopharma Joachim Ganzer KG, Reinbek, German			X				x	
Wahn, 2009, Denmark & France	X							X		X			X	X						Approx 5-6 m	Aqueous mixture of 5 grass pollen extracts (orchard, meadow, perennial rye, sweet vernal, and timothy; Stallergenes SA, Antony, France) (300 IR)	X	X					X	

Table 1c. Characteristics of ILIT studies (n = 2)

Study (First author, year, country)	Allergen(s) type								Allergen number		Route AIT		Comparator			AIT Protocol												Short term effectiveness			Long term effectiveness	SAFETY			Quality of life	
	Grass pollens	Tree pollens	Weeds	Moulds	House dust mite	Cat	Dog	Other (s)	single	Multiple	SCIT	SLIT	ILIT	placebo	routine care	active	Pre seasonal	Co-seasonal	Conventional	Cluster	Semi-rush	Short rush	Build-up mix	Duration of Rx	Product type/ Name (manufacturer)	Symptom score	Medication score	Combined score	Systemic reaction	Local reaction	Combined score		
Hylander et al, 2016, Spain	X	X							X				X	X			X			X				2 mos	aluminium hydroxide adsorbed, depot birch- or grass-pollen vaccine / Alutard (ALK Abéllo)	X	X					X	
Senti, et al, 2012, Switzerland						X			X				X	X					X		X			2 mos	recombinant major cat dander allergen Fel d 1 fused to a modular antigen transporter (MAT) vaccine (MAT–Fel d 1)/ NR (extract purchased from Stallergenes)	X *						X	X

** assessment after 300 days of discontinuation of ILIT*

***AIT**, allergen specific immunotherapy; **mo,** month; **NR**, not reported; **Rx,** treatment; **SCIT**,* subcutaneous immunotherapy; ***SLIT**, sublingual immunotherapy,* ; ***ILIT**, intralymphatic immunotherapy.*

Figure 1: PRISMA Diagram

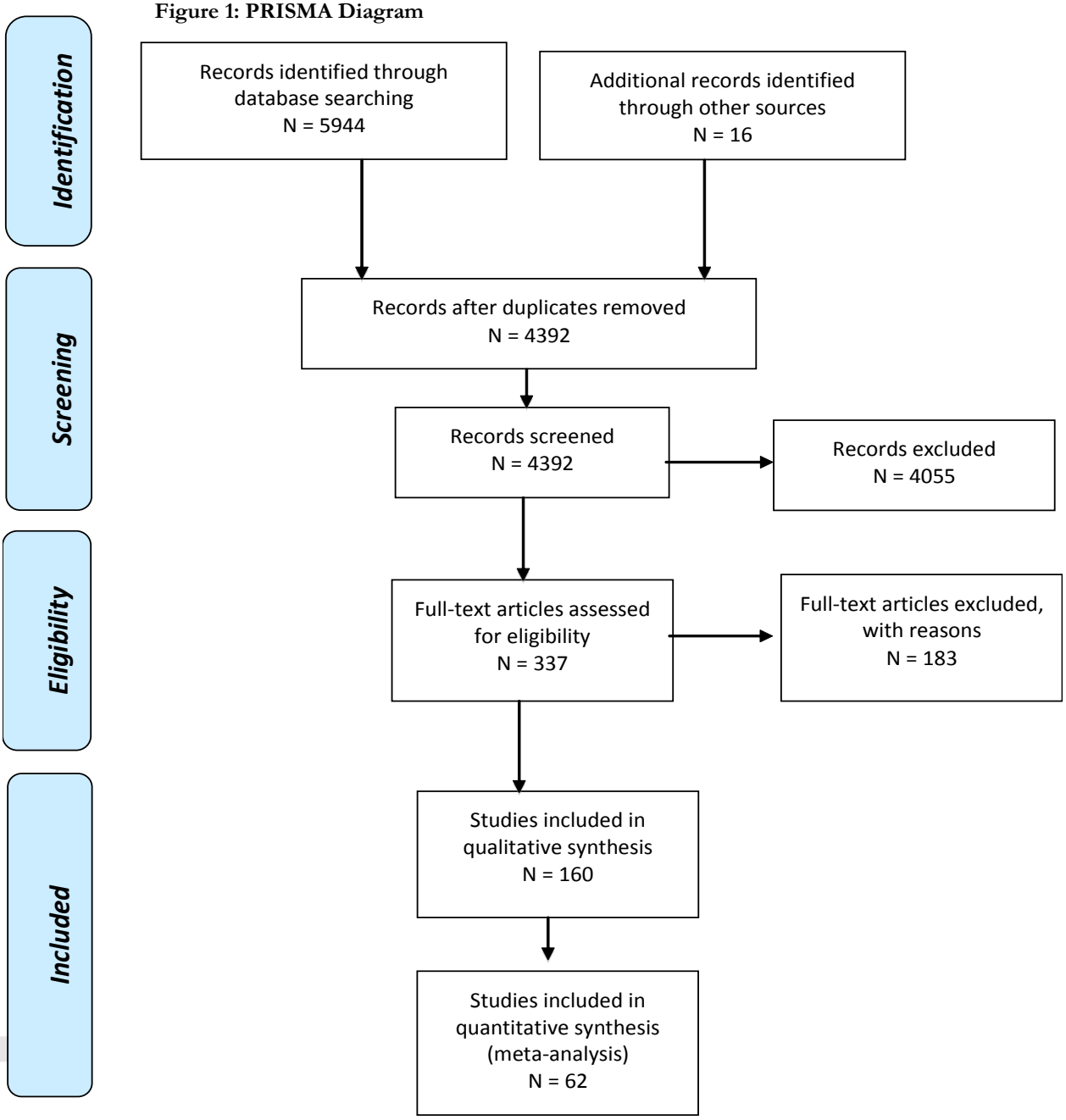
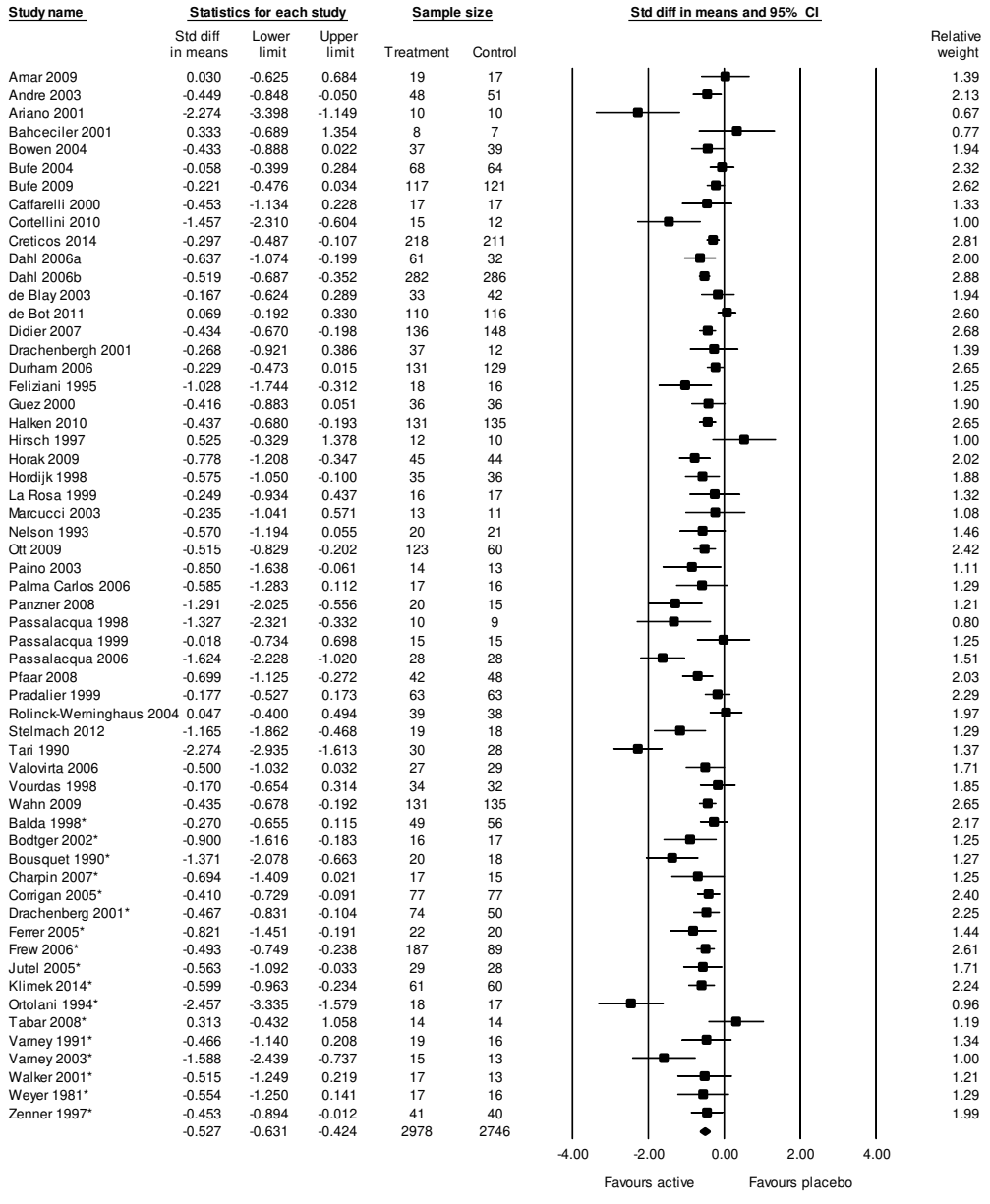


Figure 2: Meta-analysis of double-blind RCTs comparing symptom scores between AIT (SCIT or SLIT) and placebo groups (random-effects model)



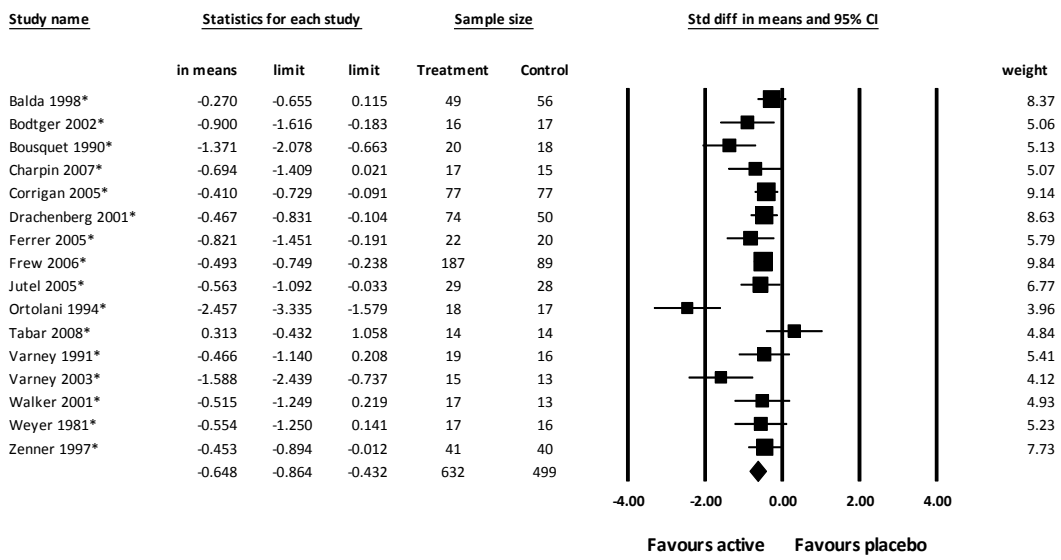
Heterogeneity: $\tau^2 = 0.090$; $\chi^2 = 173.586$, df = 57 (P<0.0001); $I^2 = 67\%$;

Test for overall effect: Z = -9.992 (P<0.0001)

**denotes SCIT studies*

Figure 3: Meta-analysis of double-blind RCTs comparing symptom scores between (a) SCIT and placebo groups and (b) SLIT and placebo group (random-effects models)

a)

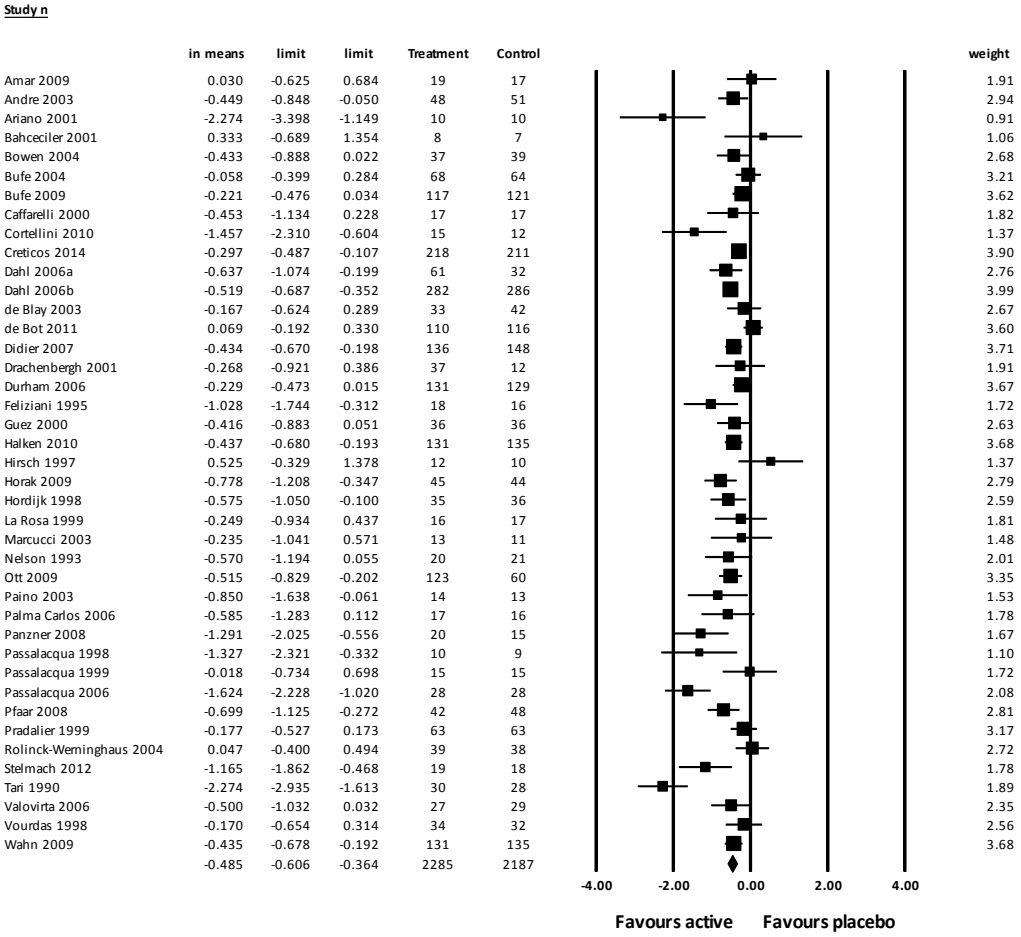


Heterogeneity: $\tau^2 = 0.106$; $\chi^2 = 39.357$, df = 15 (P<0.001); $I^2 = 62\%$;

Test for overall effect: Z = -5.875 (P<0.0001)

**denotes SCIT studies*

b)



Study n	in means	limit	limit	Treatment	Control	weight
Amar 2009	0.030	-0.625	0.684	19	17	1.91
Andre 2003	-0.449	-0.848	-0.050	48	51	2.94
Ariano 2001	-2.274	-3.398	-1.149	10	10	0.91
Bahceciler 2001	0.333	-0.689	1.354	8	7	1.06
Bowen 2004	-0.433	-0.888	0.022	37	39	2.68
Bufe 2004	-0.058	-0.399	0.284	68	64	3.21
Bufe 2009	-0.221	-0.476	0.034	117	121	3.62
Caffarelli 2000	-0.453	-1.134	0.228	17	17	1.82
Cortellini 2010	-1.457	-2.310	-0.604	15	12	1.37
Creticos 2014	-0.297	-0.487	-0.107	218	211	3.90
Dahl 2006a	-0.637	-1.074	-0.199	61	32	2.76
Dahl 2006b	-0.519	-0.687	-0.352	282	286	3.99
de Blay 2003	-0.167	-0.624	0.289	33	42	2.67
de Bot 2011	0.069	-0.192	0.330	110	116	3.60
Didier 2007	-0.434	-0.670	-0.198	136	148	3.71
Drachenbergh 2001	-0.268	-0.921	0.386	37	12	1.91
Durham 2006	-0.229	-0.473	0.015	131	129	3.67
Feliziani 1995	-1.028	-1.744	-0.312	18	16	1.72
Guez 2000	-0.416	-0.883	0.051	36	36	2.63
Halken 2010	-0.437	-0.680	-0.193	131	135	3.68
Hirsch 1997	0.525	-0.329	1.378	12	10	1.37
Horak 2009	-0.778	-1.208	-0.347	45	44	2.79
Hordijk 1998	-0.575	-1.050	-0.100	35	36	2.59
La Rosa 1999	-0.249	-0.934	0.437	16	17	1.81
Marcucci 2003	-0.235	-1.041	0.571	13	11	1.48
Nelson 1993	-0.570	-1.194	0.055	20	21	2.01
Ott 2009	-0.515	-0.829	-0.202	123	60	3.35
Paino 2003	-0.850	-1.638	-0.061	14	13	1.53
Palma Carlos 2006	-0.585	-1.283	0.112	17	16	1.78
Panzner 2008	-1.291	-2.025	-0.556	20	15	1.67
Passalacqua 1998	-1.327	-2.321	-0.332	10	9	1.10
Passalacqua 1999	-0.018	-0.734	0.698	15	15	1.72
Passalacqua 2006	-1.624	-2.228	-1.020	28	28	2.08
Pfaar 2008	-0.699	-1.125	-0.272	42	48	2.81
Pradalier 1999	-0.177	-0.527	0.173	63	63	3.17
Rolinck-Werninghaus 2004	0.047	-0.400	0.494	39	38	2.72
Stelmach 2012	-1.165	-1.862	-0.468	19	18	1.78
Tari 1990	-2.274	-2.935	-1.613	30	28	1.89
Valovirta 2006	-0.500	-1.032	0.032	27	29	2.35
Vourdas 1998	-0.170	-0.654	0.314	34	32	2.56
Wahn 2009	-0.435	-0.678	-0.192	131	135	3.68
	-0.485	-0.606	-0.364	2285	2187	

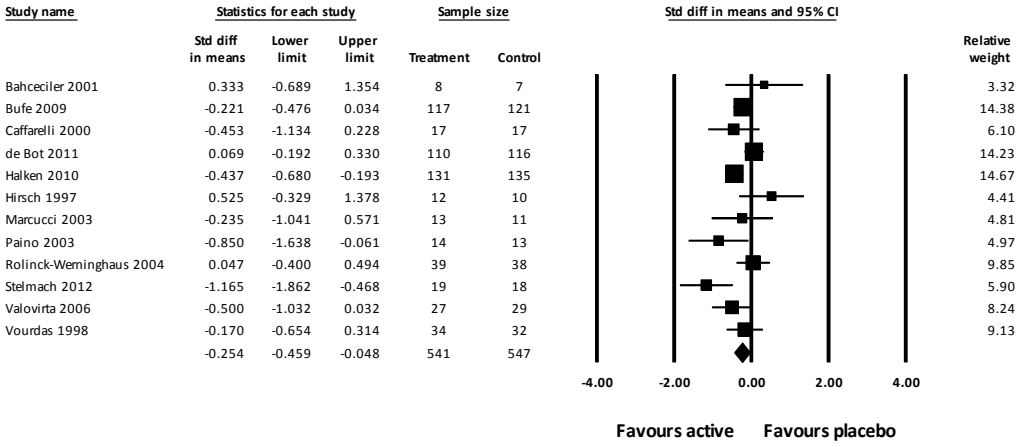
Heterogeneity: $\tau^2 = 0.088$; $\chi^2 = 129.171$, df = 40 (P<0.0001); $I^2 = 69\%$;

Test for overall effect: Z = -7.855 (P<0.0001)

**denotes SCIT studies*

Figure 4: Meta-analysis of double-blind RCTs comparing symptom scores between AIT (SCIT or SLIT) and placebo group in (a) those <18 years old and (b) those≥18 years old (random-effects models)

a)



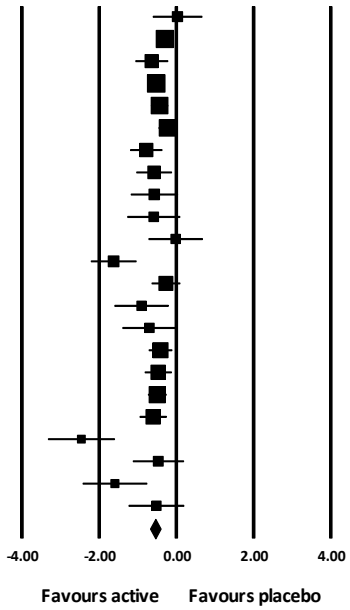
Study name	Std diff in means	Lower limit	Upper limit	Treatment	Control	Relative weight
Bahceciler 2001	0.333	-0.689	1.354	8	7	3.32
Bufe 2009	-0.221	-0.476	0.034	117	121	14.38
Caffarelli 2000	-0.453	-1.134	0.228	17	17	6.10
de Bot 2011	0.069	-0.192	0.330	110	116	14.23
Halken 2010	-0.437	-0.680	-0.193	131	135	14.67
Hirsch 1997	0.525	-0.329	1.378	12	10	4.41
Marcucci 2003	-0.235	-1.041	0.571	13	11	4.81
Paino 2003	-0.850	-1.638	-0.061	14	13	4.97
Rolinck-Werninghaus 2004	0.047	-0.400	0.494	39	38	9.85
Stelmach 2012	-1.165	-1.862	-0.468	19	18	5.90
Valovirta 2006	-0.500	-1.032	0.032	27	29	8.24
Vourdas 1998	-0.170	-0.654	0.314	34	32	9.13
	-0.254	-0.459	-0.048	541	547	

Heterogeneity: $\tau^2 = 0.059$; $\chi^2 = 24.209$, df = 11 (P<0.012); $I^2 = 54\%$;

Test for overall effect: Z = -2.423 (P<0.015)

b)

Study name	Statistics for each study			Sample size		Relative weight
	Std diff in means	Lower limit	Upper limit	Treatment	Control	
Amar 2009	0.030	-0.625	0.684	19	17	2.93
Creticos 2014	-0.297	-0.487	-0.107	218	211	7.45
Dahl 2006a	-0.637	-1.074	-0.199	61	32	4.62
Dahl 2006b	-0.519	-0.687	-0.352	282	286	7.70
Didier 2007	-0.434	-0.670	-0.198	136	148	6.93
Durham 2006	-0.229	-0.473	0.015	131	129	6.82
Horak 2009	-0.778	-1.208	-0.347	45	44	4.69
Hordijk 1998	-0.575	-1.050	-0.100	35	36	4.27
Nelson 1993	-0.570	-1.194	0.055	20	21	3.11
Palma Carlos 2006	-0.585	-1.283	0.112	17	16	2.68
Passalacqua 1999	-0.018	-0.734	0.698	15	15	2.59
Passalacqua 2006	-1.624	-2.228	-1.020	28	28	3.24
Balda 1998*	-0.270	-0.655	0.115	49	56	5.17
Bodtger 2002*	-0.900	-1.616	-0.183	16	17	2.59
Charpin 2007*	-0.694	-1.409	0.021	17	15	2.59
Corrigan 2005*	-0.410	-0.729	-0.091	77	77	5.92
Drachenberg 2001*	-0.467	-0.831	-0.104	74	50	5.41
Frew 2006*	-0.493	-0.749	-0.238	187	89	6.68
Klimek 2014*	-0.599	-0.963	-0.234	61	60	5.40
Ortolani 1994*	-2.457	-3.335	-1.579	18	17	1.91
Varney 1991*	-0.466	-1.140	0.208	19	16	2.81
Varney 2003*	-1.588	-2.439	-0.737	15	13	2.00
Walker 2001*	-0.515	-1.249	0.219	17	13	2.50
	-0.559	-0.696	-0.421	1557	1406	

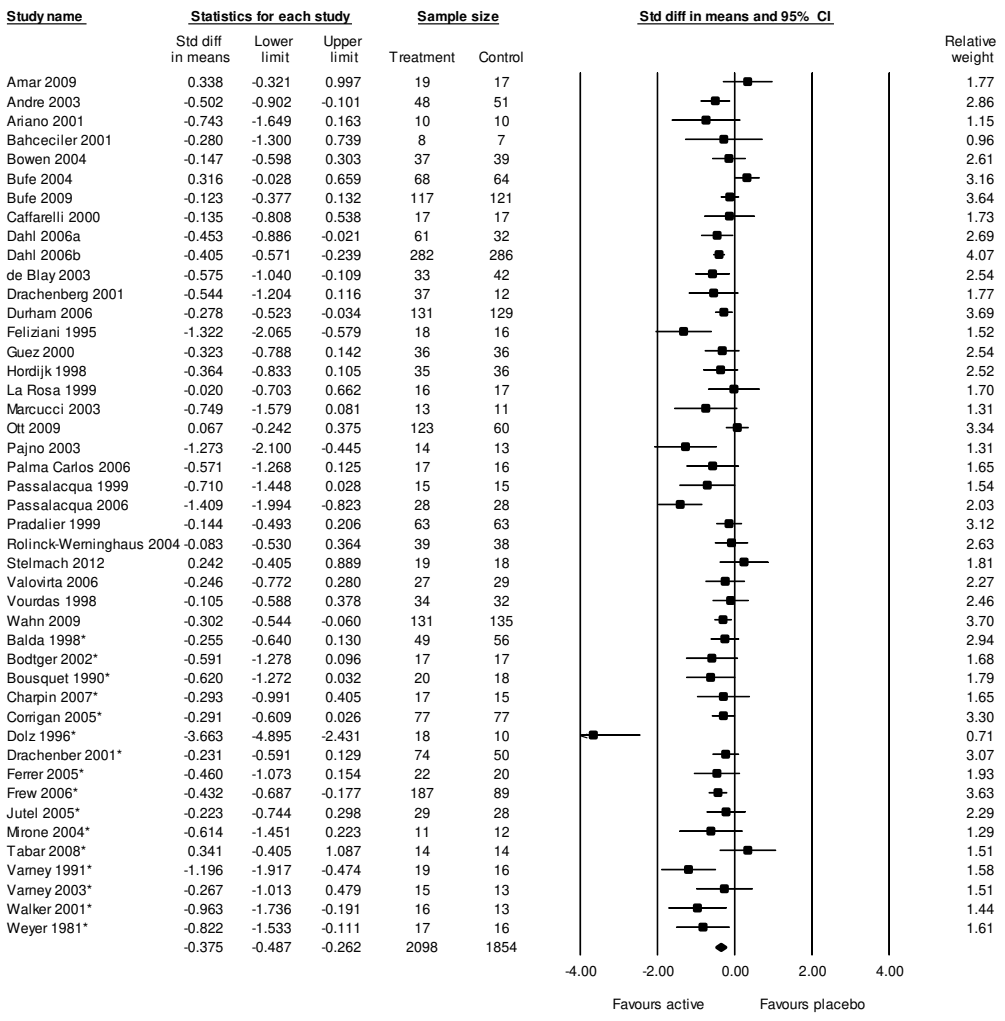


Heterogeneity: $\tau^2 = 0.057$; $\chi^2 = 57.748$ df = 22 (P<0.0001); $I^2 = 62\%$;

Test for overall effect: Z = -7.969 (P<0.0001)

**denotes SCIT studies*

Figure 5: Meta-analysis of double-blind RCTs studies comparing medication scores between AIT (SCIT or SLIT) and placebo groups (random-effects model)



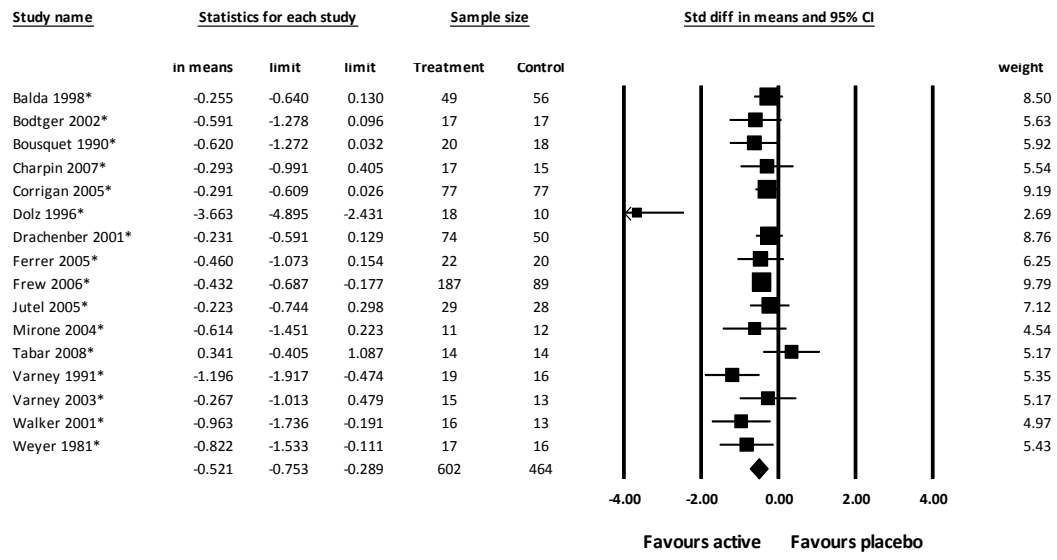
Heterogeneity: $\tau^2 = 0.074$; $\chi^2 = 110.337$, df = 44 (P<0.0001); $I^2 = 60\%$;

Test for overall effect: Z = -6.502 (P<0.0001)

**denotes SCIT studies*

Figure 6: Meta-analysis of double-blind RCTs comparing medication scores between (a) SCIT and placebo groups and (b) SLIT and placebo groups (random-effects models)

a)

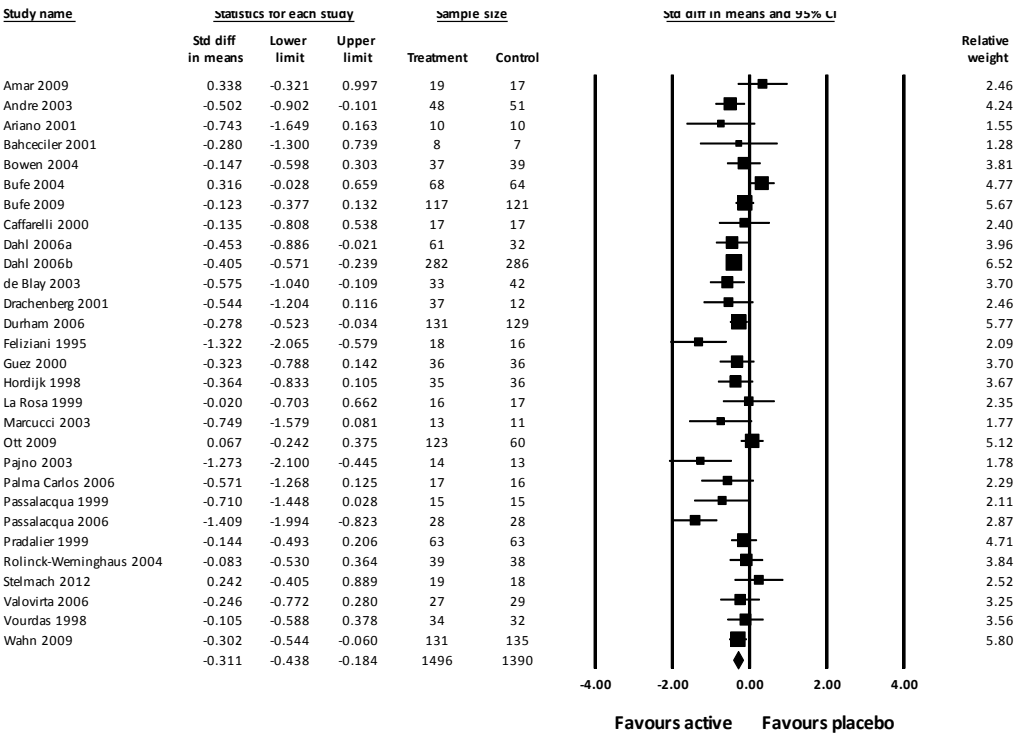


Heterogeneity: $\tau^2 = 0.126$; $\chi^2 = 42.241$, df = 15 (P<0.0001); $I^2 = 64\%$;

Test for overall effect: Z = -4.399 (P<0.0001)

**denotes SCIT studies*

b)

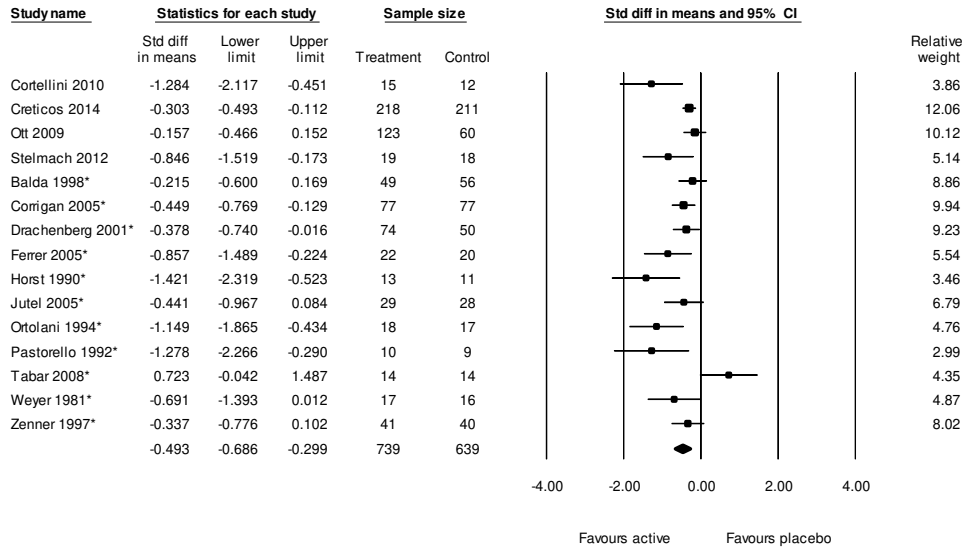


Study name	Statistics for each study			Sample size		Std diff in means and 95% CI	Relative weight
	Std diff in means	Lower limit	Upper limit	Treatment	Control		
Amar 2009	0.338	-0.321	0.997	19	17		2.46
Andre 2003	-0.502	-0.902	-0.101	48	51		4.24
Ariano 2001	-0.743	-1.649	0.163	10	10		1.55
Bahceciler 2001	-0.280	-1.300	0.739	8	7		1.28
Bowen 2004	-0.147	-0.598	0.303	37	39		3.81
Bufe 2004	0.316	-0.028	0.659	68	64		4.77
Bufe 2009	-0.123	-0.377	0.132	117	121		5.67
Caffarelli 2000	-0.135	-0.808	0.538	17	17		2.40
Dahl 2006a	-0.453	-0.886	-0.021	61	32		3.96
Dahl 2006b	-0.405	-0.571	-0.239	282	286		6.52
de Blay 2003	-0.575	-1.040	-0.109	33	42		3.70
Drachenberg 2001	-0.544	-1.204	0.116	37	12		2.46
Durham 2006	-0.278	-0.523	-0.034	131	129		5.77
Feliziani 1995	-1.322	-2.065	-0.579	18	16		2.09
Guez 2000	-0.323	-0.788	0.142	36	36		3.70
Hordijk 1998	-0.364	-0.833	0.105	35	36		3.67
La Rosa 1999	-0.020	-0.703	0.662	16	17		2.35
Marcucci 2003	-0.749	-1.579	0.081	13	11		1.77
Ott 2009	0.067	-0.242	0.375	123	60		5.12
Pajno 2003	-1.273	-2.100	-0.445	14	13		1.78
Palma Carlos 2006	-0.571	-1.268	0.125	17	16		2.29
Passalacqua 1999	-0.710	-1.448	0.028	15	15		2.11
Passalacqua 2006	-1.409	-1.994	-0.823	28	28		2.87
Pradalier 1999	-0.144	-0.493	0.206	63	63		4.71
Rolinck-Werninghaus 2004	-0.083	-0.530	0.364	39	38		3.84
Stelmach 2012	0.242	-0.405	0.889	19	18		2.52
Valovirta 2006	-0.246	-0.772	0.280	27	29		3.25
Vourdas 1998	-0.105	-0.588	0.378	34	32		3.56
Wahn 2009	-0.302	-0.544	-0.060	131	135		5.80
	-0.311	-0.438	-0.184	1496	1390		

Heterogeneity: $\tau^2 = 0.057$; $\chi^2 = 64.535$, df = 28 (P<0.0001); $I^2 = 57\%$;

Test for overall effect: Z = -4.805 (P<0.0001)

Figure 7: Meta-analysis of double-blind RCTs studies comparing combined symptom and medication scores between AIT (SCIT or SLIT) and placebo groups (random-effects model)



Heterogeneity: $\tau^2 = 0.071$; $\chi^2 = 33.631$, df = 14 (P<0.002); $I^2 = 58\%$;

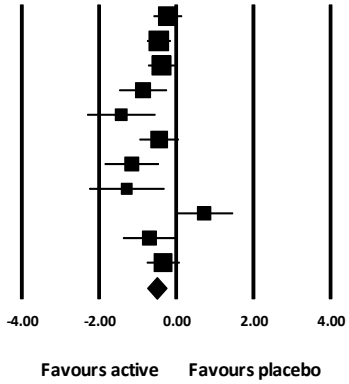
Test for overall effect: Z = -4.997 (P<0.001)

**denotes SCIT studies*

Figure 8: Meta-analysis of double-blind RCTs comparing combined symptom and medication scores between (a) SCIT and placebo groups and (b) SLIT and placebo groups (random-effects models)

a)

Study name	Statistics for each study			Sample size		Std diff in means and 95% CI	Relative weight
	Std diff in means	Lower limit	Upper limit	Treatment	Control		
Balda 1998*	-0.215	-0.600	0.169	49	56		12.39
Corrigan 2005*	-0.449	-0.769	-0.129	77	77		13.59
Drachenberg 2001*	-0.378	-0.740	-0.016	74	50		12.81
Ferrer 2005*	-0.857	-1.489	-0.224	22	20		8.32
Horst 1990*	-1.421	-2.319	-0.523	13	11		5.44
Jutel 2005*	-0.441	-0.967	0.084	29	28		9.92
Ortolani 1994*	-1.149	-1.865	-0.434	18	17		7.26
Pastorello 1992*	-1.278	-2.266	-0.290	10	9		4.75
Tabar 2008*	0.723	-0.042	1.487	14	14		6.71
Weyer 1981*	-0.691	-1.393	0.012	17	16		7.41
Zenner 1997*	-0.337	-0.776	0.102	41	40		11.40
	-0.514	-0.766	-0.261	364	338		



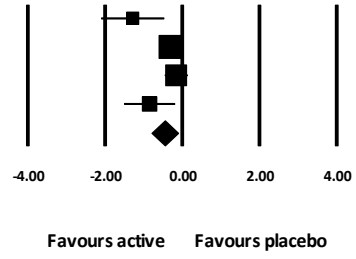
Heterogeneity: $\tau^2 = 0.096$; $\chi^2 = 23.777$, df = 10 (P<0.008); $I^2 = 58\%$;

Test for overall effect: Z = -3.984 (P<0.0001)

**denotes SCIT studies*

b)

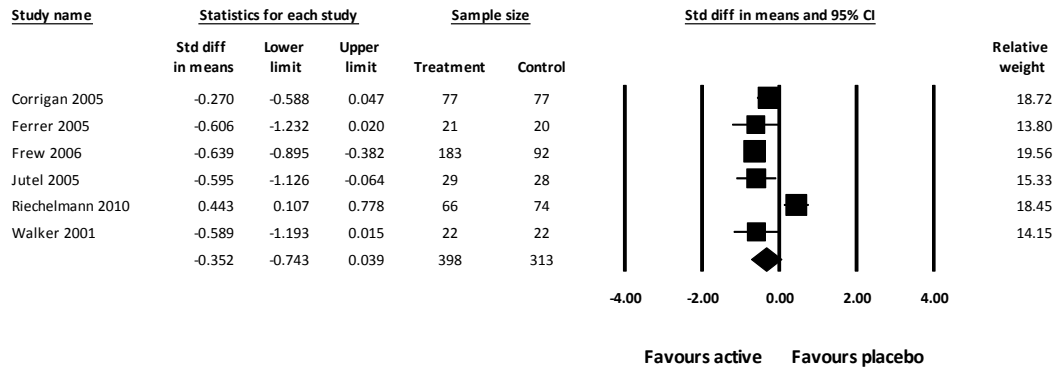
Study name	Statistics for each study			Sample size		Std diff in means and 95% CI	
	in means	limit	limit	Treatment	Control		weight
Cortellini 2010	-1.284	-2.117	-0.451	15	12		12.33
Creticos 2014	-0.303	-0.493	-0.112	218	211		38.76
Ott 2009	-0.157	-0.466	0.152	123	60		32.48
Stelmach 2012	-0.846	-1.519	-0.173	19	18		16.43
	-0.466	-0.810	-0.121	375	301		



Heterogeneity: $\tau^2 = 0.070$; $\chi^2 = 8.584$, df = 3 (P<0.035); $I^2 = 65\%$;

Test for overall effect: Z = -2.648 (P<0.008)

Figure 9: Meta-analysis of double-blind RCTs comparing quality of life scores between SCIT and placebo groups (random-effects models)



Heterogeneity: $\tau^2 = 0.186$; $\chi^2 = 28.432$, df = 5 (P<0.0001); $I^2 = 82\%$;

Test for overall effect: Z = -1.764 (P<0.078)